Dawn Merton Boothe

Small Animal Clinical Pharmacology and Therapeutics

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To Harry, who has made this possible; to Ashley and Matthew, who have made it much more fun; and to Wolf, who we miss, Stanley, who makes us laugh, and all other four-footed family members who make this book important.

And God made the beast of the earth according to its kind,
and cattle according to its kind,
and every thing that creeps on the earth after its kind:
and God saw that it was good.
And God said, Let us make man in our image,
according to our likeness:
and let them have dominion over the fish of the sea,
and over the birds of the air,
and over the cattle, and over all the earth,
and over every creeping thing that creeps on the earth.
Genesis 1:25,26 (KJV)

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Preface

Despite its young age, the discipline of clinical pharmacology has filled a void in the provision of health care. The discipline provides guidance to regulatory agencies, industry research and development, and academic research, teaching, and service. In practice, clinical pharmacology has improved rational drug therapy by emphasizing topics such as individualization of drug therapy, drug interactions, adverse drug reactions, and evidence-based medicine. Clinical pharmacology continues to provide critical input in emerging disciplines such as pharmacovigilance, pharmacogenetics, and pharmacoeconomics.

This text is intended to be the first of its kind in the veterinary profession: a text that bridges the basic science of pharmacology, a drug-based discipline, and the clinical science of therapeutics, a disease-based discipline. The text, limited to small animal medicine, is intended to consolidate information generated during the past several decades while validating it with either scientific reports or clinical experience. Foremost, the text is intended to lay the foundation for future assimilation and dispersal of knowledge in the rapidly growing disciplines of veterinary clinical pharmacology and therapeutics.

As the science of therapeutics, the practice of clinical pharmacology requires a knowledge base in the physiologic processes targeted by drugs and the pathophysiologic processes they are intended to correct. This approach is reflected in the organization of the book.

The initial section of the text deals with principles of pharmacology. These principles apply throughout and include topics such as the role of pharmacokinetics in the design of dosing regimens and the impact of patient, disease, and drug factors in therapeutic failure or adverse drug reactions. As such, this section should be read prior to any other chapters. The remainder of the book addresses those drugs used to treat or prevent diseases of small animals. Drugs that influence multiple body systems (e.g., fluid or blood component and drugs that control inflammation or pain) are addressed in the second section of this text, with each chapter dedicated to a drug category. The third section is organized using a body systems approach. The final section consists of appendices intended to facilitate rational drug use.

Within each chapter, the clinical pharmacology of each drug or drug class is discussed. This requires and thus begins with a review of the physiologic processes targeted by drugs. Discussion of mechanisms of action and pharmacologic effects facilitate proper drug selection and anticipation of adverse reactions. Mechanisms of resistance are included in chapters that address chemotherapy. The disposition or pharmacokinetics of drugs provides a basis for modifying dosing regimens when necessary to compensate for drug, host, or disease factors that might alter response to therapy. Drug interactions and adverse drug reactions and their avoidance and treatment are included to minimize therapeutic failure. A list of available formulations is provided in most chapters.

The discussion of clinical pharmacology is followed by a disease-based discussion of therapy, with a focus on drug use. A review is given of the pathophysiologic features of the disease process as it relates to drug selection. Although treatment focuses on drugs, adjuvant therapy is also delineated. Means of monitoring response to therapy and alternative therapies are often provided. Recommended therapies are often backed up by reports of clinical trials. Each chapter is supported by a table of dosing regimens.

References were not originally intended to be included, in part because of the lack of scientific reports for much of the information. However, the discipline of clinical pharmacology has rapidly become a state-of-the-art science in veterinary medicine, and, as such, new information is being generated through scientific reports. Thus, references have been included at the end of each chapter, although each list is not exhaustive.

This book attempts to address most small animal illnesses in a comprehensive fashion. Emergency and critical therapies are not addressed as a separate chapter; rather, selected syndromes that require emergency care are included in appropriate chapters. The impact of antimicrobial resistance on treatment of infectious diseases has led to an increased awareness of proper antibiotic use and a willingness to follow proper principles of therapy. Thus, multiple chapters address this topic, with one chapter dedicated to each of the following: the principles of antimicrobial therapy, antibacterial drugs, and a predominantly systems approach to treatment of bacterial infections. Information that directs the selection of drugs and design of antimicrobial dosing regimens includes a table of minimum inhibitory concentrations, breakpoint concentrations, and peak plasma drug concentrations achieved after drug administration. Additional chapters each focus on antifungal, antiprotozoal and antiviral therapy. A chapter is also dedicated to disinfectant and antiseptic therapy, a topic often neglected when considering control of infectious diseases. The central nervous system is addressed in several chapters, including anesthetics, chemical restraints, control of pain, anticonvulsant therapy, and drugs that modify behavior. Because glucocorticoid therapy is complex, a separate chapter is dedicated to this topic. Chapters that address advancing therapies in veterinary medicine include control of pain, control of inflammation, biological response modifiers, recombinant drug therapy and behavior-modifying drugs. For selected diseases, nutritional and "nutraceutical" products may also be addressed.

DAWN MERTON BOOTHE, D.V.M.

Acknowledgments

The seeds that ultimately led to my commitment to veterinary clinical pharmacology clearly were planted during my second year veterinary pharmacology course. I can still envision my mentor, Dr. William Jenkins, presenting his favorite drugs (there were many) in a manner that not only made sense but facilitated my understanding of the pathophysiologic aspects of disease. I have been fortunate not only to have been mentored by a truly gifted individual but also to be able to publicly express my gratitude to him through the fruits of his labor, this textbook. Gratitude is offered not only for his excellence as a teacher but also for his gentle, persistent, and wise mentoring. My enjoyment of internal medicine was the determining role in my commitment to clinical pharmacology. Without the superb clinical expertise and guidance of the small animal clinical faculty at both Auburn University (especially Drs. Ralph Henderson, Ray Dillon, Guy Pidgeon, and Charles Knecht) and Texas A&M University, I would not have grasped the intricate relationship between the pathophysiologic aspects of diseases and the rational use of drugs.

The contributors to this book include those individuals whose prior and current efforts have generated scientific data supporting drug therapy in small animals. These include Dr. Lloyd Davis, generally recognized as the "father" of clinical pharmacology, and the charter members of the American College of Veterinary Clinical Pharmacology (ACVCP), Drs. Arthur Aronson, William Jenkins, Tom Powers, and Charles Short (of Louisiana State University). Their foresight preceded the formation of ACVCP by over a decade, and the veterinary literature is replete with their contributions to the discipline. Their work continues through the efforts of my peers, veterinary clinical pharmacologists who currently hold positions in academia, industry, regulatory agencies, and private practice. The information in this text is largely drawn from the data generated by each of these individuals, either directly or in collaboration with others.

Acknowledgments would be incomplete without recognition of those individuals who provided relief in my work environment, allowing redirection of my efforts toward this text. This includes Drs. Sarah Jones and Albert Boeckh, and their predecessor, Dr. Katrina Mealey (now a diplomate of ACVCP and ACVIM), who as clinical pharmacology residents not only shared my workload but more importantly offered new perspectives on the therapeutic management of small animal diseases. Thanks also to Dr. Glen Laine, the current head of our department, who maintains high standards while encouraging his faculty to pursue activities that facilitate the application of research to the teaching and service aspects of our profession. Dr. Debbie Kochevar and Dr. Gordon Brumbaugh, also diplomates of ACVCP, have been and continue to be an enjoyable, knowledgeable sounding board for topics addressed in this text as well as for concepts related to the teaching of clinical pharmacology.

Several authors were kind enough to contribute to this text in their area of expertise, i.e., fluid therapy (Dr. Mike Willard), antiprotozoal and parasiticides (Dr. Randy Lynn), reproductive therapy (Dr. Janice Cain), immunomodulatory therapy (Dr. Steve Kruth), recombinant product therapy (Dr. Debbie Kochevar), anesthetics (Dr. Elizabeth Martinez), skeletal muscle relaxants (Dr. Elizabeth Martinez and Dr. Katrina Mealey), and treatment of renal disease (Dr. India Lane). The staff members at W.B. Saunders are to be recognized for their patience when encountering the inevitable delays in manuscript submission, for the frustrations that no doubt were encountered while interpreting my corrections, and for their efficient guidance in the completion of this project.

Finally and foremost, without the encouragement, help, and support provided by my husband, Harry W. Boothe Jr., my father, H. Lewis Merton, and parents-in-law, Harry W. Boothe and Alberta Boothe, this text would remain the idea it has always been rather than the reality it has become. To all, I am most grateful.

NOTICE

Veterinary Medicine is an ever-changing field. Standard safety precautions must be followed, but as new research and clinical experience broaden our knowledge, changes in treatment and drug therapy may become necessary or appropriate. Readers are advised to check the most current product information provided by the manufacturer of each drug to be administered to verify the recommended dose, the method and duration of administration, and the contraindications. It is the responsibility of the treating veterinarian, relying on experience and the knowledge of the animal, to determine dosages and the best treatment for the animal. Neither the publisher nor the editor assumes any responsibility for any injury and/or damage to animals or property arising from this publication.

THE PUBLISHER

Contents

SECTION ONE

INTRODUCTION TO DRUG USE IN SMALL ANIMALS 1

1
Principles of Drug Therapy 3
Dawn Merton Boothe

2
Factors Affecting Drug Disposition and Extrapolation of Dosing Regimens 18
Dawn Merton Boothe

3
Drug-Induced Diseases 41
Dawn Merton Boothe

4
Therapeutic Drug Monitoring 60
Dawn Merton Boothe

SECTION TWO

A THERAPEUTICS APPROACH 73

5
Fluids, Electrolytes, and Acid-Base Therapy 75
Michael D. Willard

6
Therapy with Blood and Blood Components 97
Dawn Merton Boothe

7
Drugs Acting on Blood or Blood-Forming Organs 107
Dawn Merton Boothe

8
Principles of Antimicrobial Therapy 125
Dawn Merton Boothe

9
Antimicrobial Drugs 150
Dawn Merton Boothe

10
Treatment of Bacterial Infections 175
Dawn Merton Boothe

11
Treatment of Fungal Infections 222
Dawn Merton Boothe

12
Antiviral Therapy 237
Dawn Merton Boothe

13
Disinfectants, Antiseptics, and Related Germicides 250
Harry W. Boothe

14
Drugs for the Treatment of Protozoal Infections 258
Randy C. Lynn

15
Drugs for the Treatment of Helminth Infections 267
Randy C. Lynn

16
Anti-inflammatory Drugs 281
Dawn Merton Boothe

17
Glucocorticoid Therapy in the Dog and Cat 313
Dawn Merton Boothe
Katrina A. Mealey

18
Chemotherapy 330
Claudia L. Barton

19
Immunomodulators or Biologic Response Modifiers: Introduction and Miscellaneous Agents **349**
Dawn Merton Boothe

20
Biologic Response Modifiers: Interferons, Interleukins, Recombinant Products, and Liposomal Products **371**
Stephen A. Kruth

21
Recombinant Biotechnology in Veterinary Therapeutics **383**
Deborah T. Kochevar

SECTION THREE
A SYSTEMS APPROACH **403**

22
Control of Pain in Small Animals: Opioid Agonists and Antagonists and Other Locally and Centrally Acting Analgesics .. **405**
Dawn Merton Boothe

23
Anesthetic Agents **425**
Elizabeth A. Martinez

24
Anticonvulsants and Other Neurologic Therapies in Small Animals **431**
Dawn Merton Boothe

25
Drugs That Modify Animal Behavior **457**
Dawn Merton Boothe

26
Muscle Relaxants **473**
Elizabeth A. Martinez
Katrina A. Mealey

27
Gastrointestinal Pharmacology **482**
Dawn Merton Boothe

28
Drugs Affecting the Kidneys and Urination **515**
Dawn Merton Boothe

29
Treatment of Urinary Disorders **528**
India F. Lane

30
Therapy of Cardiovascular Diseases **553**
Dawn Merton Boothe

31
Drugs Affecting the Respiratory System **602**
Dawn Merton Boothe

32
Drug Therapy for Endocrinopathies **624**
Dawn Merton Boothe

33
Dermatologic Therapy **654**
Dawn Merton Boothe

34
Rational Use of Reproductive Hormones **677**
Janice L. Cain

Appendices **691**

Index **771**

SECTION ONE

Introduction to Drug Use in Small Animals

Principles of Drug Therapy

1

Dawn Merton Boothe

DOSE-RESPONSE RELATIONSHIP
DETERMINANTS OF DRUG DISPOSITION
Drug Movement
  Plasma Drug Concentration Versus Time Curve
  Mechanisms of Drug Movement
Determinants of Drug Disposition
  Absorption
  Distribution
  Metabolism
  Renal and Biliary Excretion
  Elimination
FIXED DOSING REGIMENS
Dose
Interval
Accumulation

DOSE-RESPONSE RELATIONSHIP

The intent of drug therapy is to induce a desired pharmacologic response for a sufficiently long period of time while avoiding adverse drug reactions. Two types of adverse drug reactions, referred to as types A and B, can follow drug administration (Griffin, 1979; Lawson, 1982; Klassan, 1985). Type A drug reactions commonly reflect plasma drug concentrations that have exceeded the therapeutic range and entered the toxic range. Thus, these reactions are often manifested as an exaggerated but otherwise normal pharmacologic response to a drug. In contrast to type A reactions, type B adverse drug reactions are not related to the expected pharmacologic effect of the drug. They are unpredictable, not dose-dependent, and are thus difficult to avoid. For most drugs, the magnitude of pharmacologic response is proportionately related to the (log of) drug concentration at the tissue (receptor) site (Fig. 1–1). Because tissue samples cannot be collected easily, drug concentrations at the tissue site are approximated by measuring plasma drug concentrations (PDCs). The *therapeutic range* provides a target for the dosing regimen. It consists of a minimum effective PDC (trough or C_{min}), below which therapeutic failure is likely to occur; and a maximum effective PDC (peak or C_{max}), above which a type A adverse reaction (see Chapter 3) is more likely to occur (see Fig. 1–1) (Ritschel, 1992; Rollins, 1989).

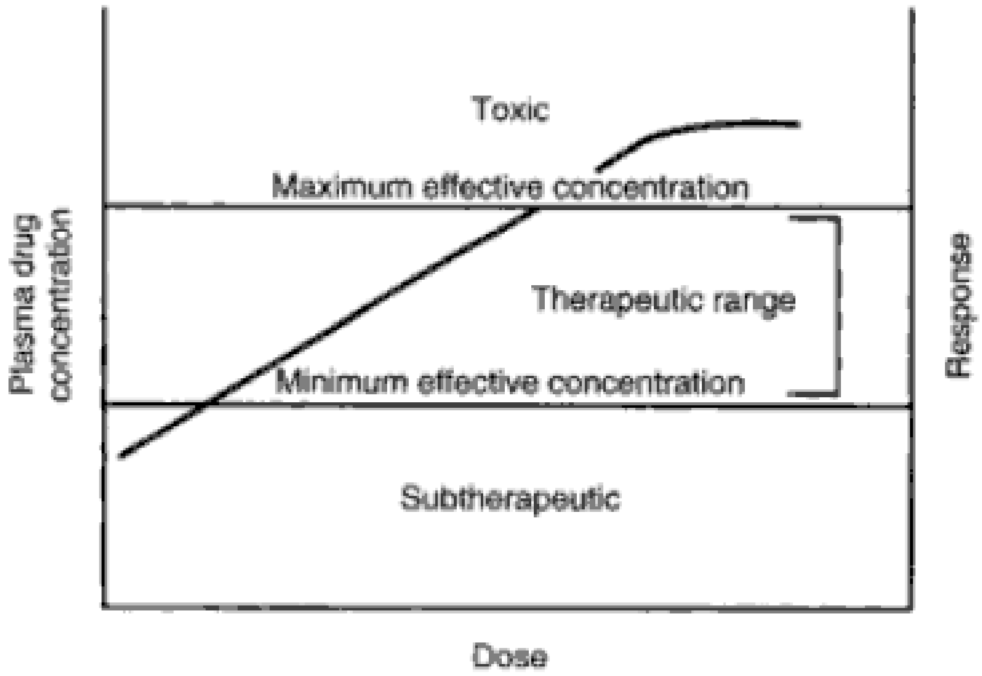
Toxic
Maximum effective concentration
Therapeutic range
Minimum effective concentration
Subtherapeutic
Plasma drug concentration
Response
Dose

Figure 1–1. The relationship among log plasma or tissue drug concentration and dose and response is generally linear.

Fixed dosing regimens are composed of a dose (e.g., mg/kg) and an interval (e.g., every 8 hours) for each route. The dose of the regimen should result in a PDC that is in the therapeutic range and stays in the range throughout most of the dosing interval. Thus, targeted peak PDCs often approximate but do not exceed C_{max}, whereas trough concentrations approximate but generally do not drop below C_{min}. It is important to recognize that a therapeutic range is a population statistic. Each animal will respond (therapeutically or adversely) at a different point in the range. Most animals will respond at some PDC within the range, but a small percentage will respond above or below the range. Therapeutic drug monitoring (see Chapter 4) is used to establish where in the therapeutic range the individual animal will respond.

The relationship between the dose of drug administered and the PDC achieved after drug administration is complex. Likewise, the determinants of dosing interval, or the time that can elapse before PDC drops below C_{min}, are also complex. Type A adverse reactions should be anticipated when doses are anecdotal rather than based on scientific, controlled studies. Yet, drug therapy may fail even if the recommended fixed dosing regimen is based on scientific data because the population samples from which inferences about the patient are based tend to be healthy and small in number. The likelihood of therapeutic success is increased if individualization of drug therapy for the patient is based on the principles of clinical pharmacology, that is, the study of drugs (Beal, 1984) and their behavior (disposition) (Baggott, 1977) in animals.

DETERMINANTS OF DRUG DISPOSITION

Drug Movement

Plasma Drug Concentration Versus Time Curve

After administration of a fixed dose of a drug, several drug movements act in concert to determine PDC (Ritschel, 1992; Rollins, 1989; Baggott, 1977; Notari, 1987) (Fig.

1–2). These movements largely, but not exclusively, depend on passive diffusion of the drug and include absorption (A) from the site of administration to systemic circulation, defined as the major vessels and well-perfused organs; distribution (D) of the drug from systemic circulation to tissues (target and nontarget) and back again; and elimination of the drug from the body by metabolism (M) and excretion (E). These drug movements are dynamic, occurring simultaneously, and their net effects determine PDC at any time during the dosing interval following administration of a fixed dose.

The movements of drug through the body are characterized by plotting drug concentrations measured after administration of a known dose against time on semilogarithmic paper (Ritschel, 1992; Rowland, 1989; Notari, 1987) (Fig. 1–3). The PDC versus time curve is linearized on semilogarithmic paper if it follows first-order kinetics, that is, a constant fraction rather than a constant amount of drug moves (is absorbed, distributed, or excreted) per unit time (see Fig. 1–3). A single component of the line (i.e., only one slope or rate) infers that only one drug movement is responsible for the change in drug concentration over time. For example, Figure 1–3*A* might represent the time course of a drug whose distribution is either limited to plasma or occurs to peripheral tissues instantaneously. The change in PDC for such a drug reflects elimination from the body (that is, hepatic or renal excretion). Drug movement in such instances is only excretion as a one-compartment open (meaning drug can move into or out of compartments) model. Figure 1–3*B* might reflect a drug whose concentration initially declines due to two drug movements: distribution into (and back from) tissues and/or excretion from the body. Once distribution equilibrium reaches steady state for such drugs, the rate of decline in PDC changes (decreases) because excretion from the body is the sole movement. This change in the rate of decline is manifested as a new, less steep slope indicative of less drug leaving the blood. Drug movement for such drugs is characterized as a two-compartment open model (Notari, 1987; Ritschel, 1992; Rowland, 1989). To distinguish the rate of each movement from the rates of other movements, each slope must be identified from the curve. Generally, computer-generated programs first "strip" and then "best fit" the curve using linear regression to determine the equation that best describes each component of the time versus PDC relationship. Intravenous (IV) drug administration yields a PDC versus time curve that begins with the highest PDC (see Fig. 1–3*A* and *B*). If a drug is given parenterally (e.g., orally, intramuscularly, subcutaneously), a third movement influencing PDC versus time curve must be considered as the drug is absorbed from the site of administration (see Fig. 1–3*B*, plot C; non-IV). Absorption is indicated by an initial increase in PDC. Distribution is often "masked" by the absorptive phase of drug movement such that elimination reflects excretion only. The rate of each drug movement (absorption, distribution, or elimination) is described by the respective slope of the line or component that comprises the movement. It is important to realize, however, that the application of a drug movement to a component of the curve is theoretical and may not actually reflect what occurs in the body. Among the more important parameters derived from pharmacokinetic analysis is the area under the concentration curve (AUC). This, in turn, is used to calculate several other pharmacokinetic parameters; clinically, it is useful for determining response to antimicrobials (Schentag 1991, Martinez 1998a). Area under the curve can be derived in several ways. The most common method is calculating it by dividing the Y intercept by the slope of the respective component. Thus, for a one-compartment model, AUC = A/α; for a two-compartment model, AUC = $A/\alpha + B/\beta$, and so on (see Fig. 1–3). This method requires that the data of the PDC versus time

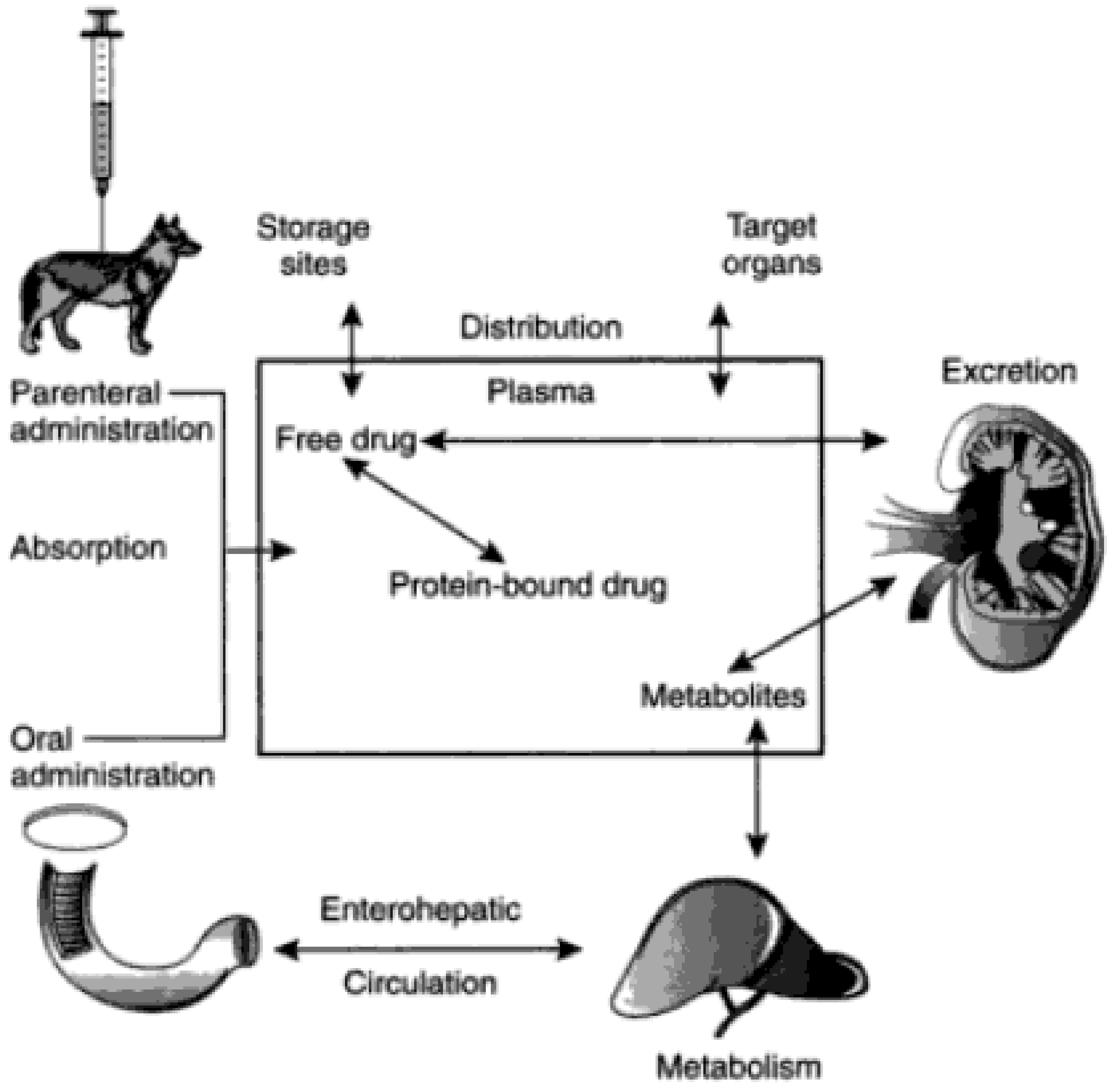

Figure 1–2. The determinants of plasma drug concentration (ADME) act in concert following administration of a fixed dose. The drug must first be absorbed, most commonly from the gastrointestinal tract. Orally administered drug passes through the liver before reaching systemic circulation (not shown). Once in circulation, drug not bound to plasma proteins (free drug) is distributed into tissues, where it can be bound to tissues or be distributed back to circulation. Elimination of the drug from the body occurs by hepatic metabolism and renal or biliary excretion of the drug or its metabolites. Excreted drugs can be passively reabsorbed by the kidney following enterohepatic circulation (bile). (Redrawn from Ettinger SJ, Feldman EF [eds]: Textbook of Veterinary Internal Medicine, 5th ed, p 294. Philadelphia, WB Saunders Company, 2000.)

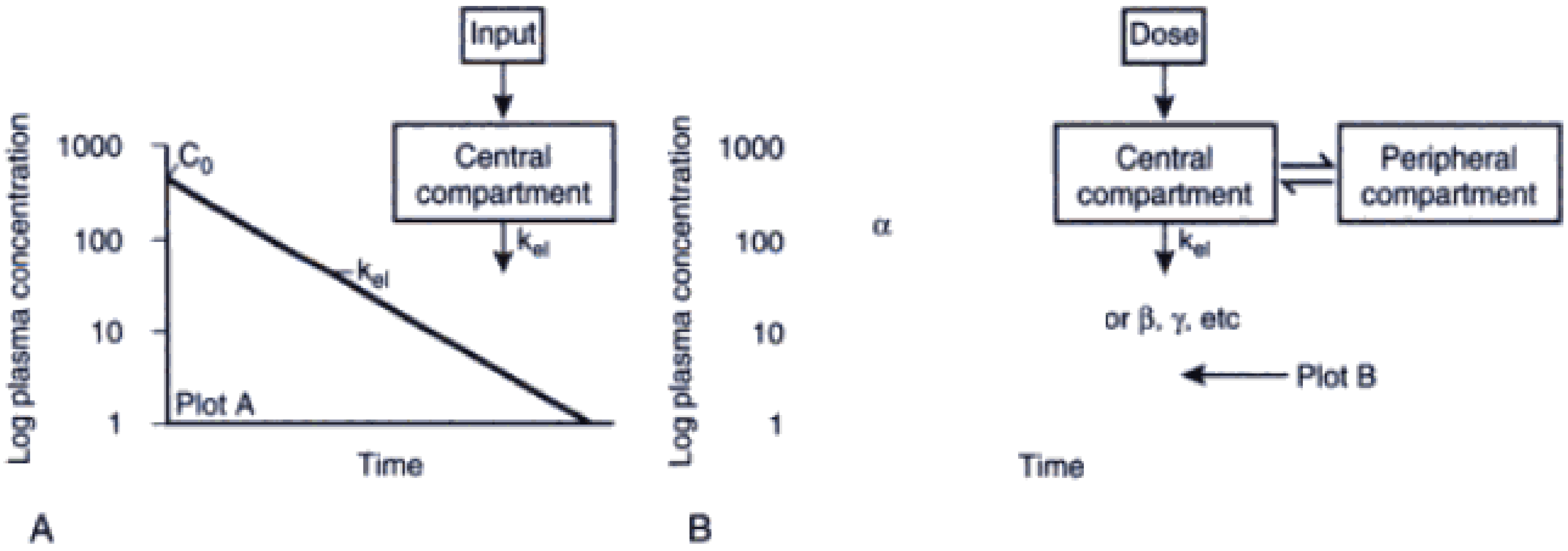

Figure 1–3. Plasma drug concentration (PDC) versus time curves. *A*, Following IV administration, a drug that fits a one-compartment open model plots as a straight line on semilogarithmic paper. There is no distribution phase, and the volume of distribution is based on PDC extrapolated *(dotted line)* back to time zero (C_0). The equation for this single component curve would be $C_p = C_0e^{-kt}$ where C_p is the plasma drug concentration at any time and t and k are the elimination rate constant (slope) of the curve. *B*, Following IV administration, a drug characterized by distribution into peripheral tissues generally results in at least two components or phases when plotted on semilogarithmic paper. The PDC declines in the first phase owing to both distribution into tissues and elimination (excretion) from the body. Once a distribution equilibrium has been reached, PDC decline is only caused by elimination (second phase or component of the curve). The two phases can be separated by stripping, most effectively accomplished by linear regression. The first (stripped and subsequently fitted) component of the curve represents distribution and the slope (α) is the distribution rate constant. The Vd for such a drug is based on PDC after distribution, usually determined by extrapolating *(dotted line)* the terminal or elimination phase of the PDC versus time curve (B on plot B). The slope of the second phase of the curve is the elimination rate constant (β or k_{el}). The equation for the curve represented by plot B (two components) would be $C_p = Ae^{-\alpha t} + Be^{-\beta t}$. The second PDC versus time curve (Plot C, Fig. B) results from oral (or other extravascular route) administration of the same dose of drug. The upswing of the plasma drug concentration versus time curve reflects first-order input (a constant fraction is absorbed per unit time) as well as distribution and elimination of the absorbed drug. The absorption rate constant (k_a, not shown) can be derived from the upswing of the curve, but only after the elimination component of the curve has been mathematically stripped. Generally, the distribution phase of non-IV doses is masked by the absorptive phase. The equation of extravascular PDC versus time curves follows the general equation: $C_p = Be^{-\alpha t}$-$Ae^{-ka\,t}$ where A is the extrapolated drug concentration from the absorptive phase of the curve. Bioavailability (F) of the drug would be determined from the ratio of the area under the curve measured from the extravascular dose *(dotted line* and *shaded area)* and the IV dose.

curve be "fit" or forced into a model (e.g., one compartment, two compartments). If the model does not fit the data very well, the pharmacokinetic parameters derived from the model do not accurately represent the data. An alternative method for calculating AUC is based on the trapezoidal method (Gibaldi, 1982, 1985). For this method, a seizure of trapezoids is calculated based on each time point. The trapezoids are added together to determine AUC. From this noncompartmental method, other model-independent parameters (e.g., mean resident time) can be calculated (Martinez, 1998b). The advantage of such methods is that data are not forced to fit a model, which may minimize error introduced by data manipulation.

Mechanisms of Drug Movement

Each drug movement (and thus each slope of the PDC versus time curve) is affected by a number of physiologic factors, the most important being the rate and extent of passive diffusion. Lipid solubility, molecular weight, and drug pK_a (a measure of strength of an acid) are important determinants of the rate and extent of passive diffusion. They are characteristic of the chemical structure of the drug and thus cannot be easily altered (Ritschel, 1992; Rowland, 1989). The concentration gradient of non-ionized drug across the site of drug movement is one of the most important determinants of passive drug diffusion, and this can be manipulated to some degree. The easiest way to increase passive drug movement is simply to increase the dose, which in turn increases the concentration gradient. Not all of the drug may, however, be diffusible.

A drug must be dissolved in order to passively diffuse. Passive diffusion occurs independent of any mechanism and requires no energy. Drug molecules simply move from an area of high drug concentration to one that is lower, with the rate of movement proportional to the concentration gradient of diffusible drug. Equilibrium is reached when the amount of drug moving from one area equals the amount moving in the opposite direction. The concentration of diffusible drug also will be equal in each area. Although a drug may be present both in its ionized (charged) and un-ionized state, according to the pH partition therapy (based on the Henderson-Hasselbalch equation), generally only the un-ionized drug is diffusible. Thus, drugs that are weak bases (e.g., alkyl or phenylalkylamines, pyridines, quinolines, imidazoles, piperidines, indoles, and phenothiazines) are ionized more in an acidic environment and thus are less diffusible compared to the same drug in an alkaline environment. The opposite is true of weak acids (e.g., carboxylic acids, sulfonamides, imides, phenols). Thus, weak acids are more likely to move passively when surrounded by an acidic environment (that is, weak acids are more likely than weak bases to be absorbed from the gastrointestinal tract and to be excreted rather than passively resorbed in an alkaline urine) (Notari, 1987). In its ionized form, a drug cannot traverse lipid membranes and will essentially be "trapped" in the environment. A drug is generally ionized when surrounded by an environmental pH that is more than 2 pH units greater than its pK_a if it is a weak acid or 2 pH units less than its pK_a if it is a weak base. Thus, as weak bases, orally administered aminoglycosides (pK_a 9 to 10) are predominantly ionized and trapped in the acidic environment of the gastrointestinal tract. Absorption is thus minimized. In contrast, as weak acids, the β-lactam antibiotics (e.g., amoxicillin or cephalothin) are sufficiently un-ionized that they are well absorbed orally.

In urine with an acidic pH, aminoglycosides will be ionized and will not easily penetrate bacteria but will be rapidly eliminated. β-Lactams, will, however be un-ionized, and as such they will not only penetrate bacteria more easily but they will also be passively reabsorbed from the renal tubular lumen and hence "recycled" before being excreted in the urine. Other host determinants of passive diffusion include thickness of the membrane to be traversed (i.e., edematous compared with normal tissues), surface area (e.g., small intestine vs. stomach), and temperature. As determinants of passive diffusion change in a patient, so will drug movement.

Passive diffusion is not the only method by which drugs move. All drugs move to some degree by bulk flow, that is, they move with the rest of the constituents in plasma or urine. Glomerular filtration of a drug is an example of bulk flow. Active transport is a less common method of drug movement, perhaps best exemplified by active secretion of drugs by renal tubular cells. Other examples of active drug transport include concentration of iodide by the thyroid gland; oral absorption of some β-lactams, and bacterial uptake of aminoglycosides. Pinocytosis is a rare drug movement exemplified by the uptake of vitamin B_{12} in the ileum and aminoglycosides by renal tubular cells. Finally, facilitated diffusion occurs for some drugs.

Determinants of Drug Disposition

Absorption

Most orally administered drugs reach systemic circulation after absorption from the small intestine. The rate and extent of drug absorption in the gastrointestinal tract depend on a number of host factors, most of which affect passive diffusion (Fig. 1–4) (Notari, 1987). These include gastrointestinal pH, which favors absorption of weak acids; surface area, which favors absorption in the small intestine compared with the stomach; motility, which mixes the drug, thus increasing the concentration of diffusible drug at the site of movement; permeability and thickness of the mucosal epithelium; and intestinal blood flow, which maintains the concentration gradient across the mucosal epithelium. The latter factor is important only for drugs capable of rapid transfer across the epithelium.

The percentage of an administered dose that reaches systemic circulation is referred to as *bioavailability* (F) (Ritschel, 1992; Rowland, 1989; Notari, 1987). Bioavailability is determined by measuring the area under a PDC versus time curve (AUC) after non-IV administration (see shaded area of plot C in Fig. 1–3) and comparing this number with the AUC measured after IV administration of the same dose (see Fig. 1–3). If the AUC for both curves are equal, bioavailability is 100% (F = 1). Bioavailability is used to predict drug efficacy after different routes of administration or administration of different formulations of the same drug. Bioavailability can only be determined after IV administration of a drug. The relative bioavailabilities of two different preparations of the same drug can, however, be evaluated by comparing the AUC of the two curves.

The factors that determine absorption of a drug also determine its bioavailability. In addition to the factors previously discussed, bioavailability of an orally administered drug is decreased if the drug is metabolized by intestinal epithelial cells or microbes or by the liver. Hepatic metabolism can profoundly affect the PDC of an orally administered drug. After gastrointestinal absorption, drugs enter the portal vein and then the liver (Fig. 1–5). Thus, an orally administered drug is exposed to hepatocytes before it enters the systemic circulation. Drugs characterized by a high hepatic extraction ratio (>70%) are almost completely removed from the blood by hepatocytes during the first passage of blood through the liver. As a result, after oral administration, the drug may not reach systemic circulation in concentrations sufficiently high to cause a pharmacologic response. Despite good to excellent oral absorption, such drugs are characterized by poor bioavailability and

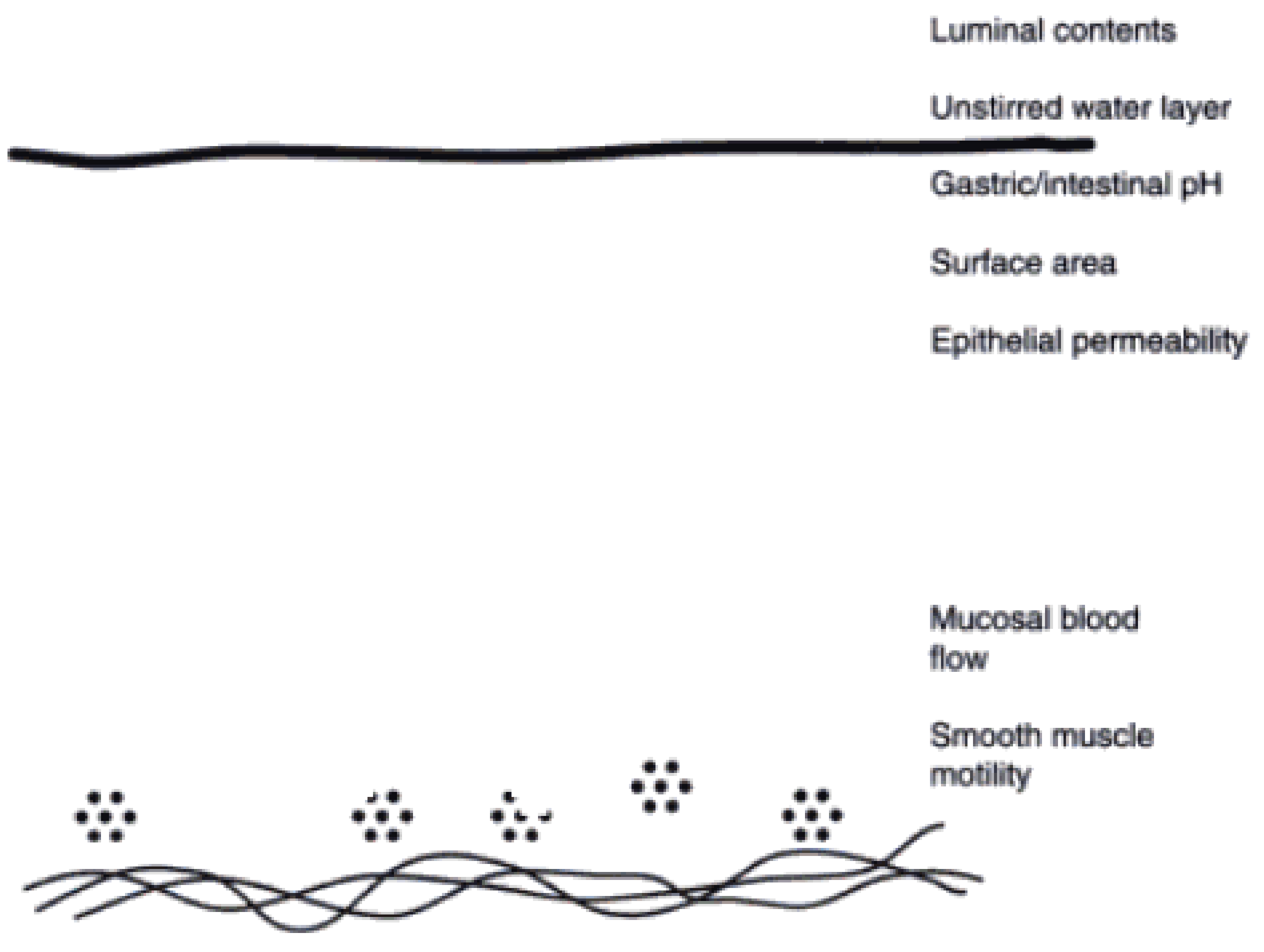

Figure 1–4. The determinants of oral drug absorption include local pH, the surface area to which the dissolved drug is presented, epithelial permeability, mucosal blood flow (particularly for drugs very rapidly absorbed), and smooth muscle motility. The drug must be dissolved (to establish a concentration gradient). Most drugs are absorbed in the small intestine because of its larger surface area.

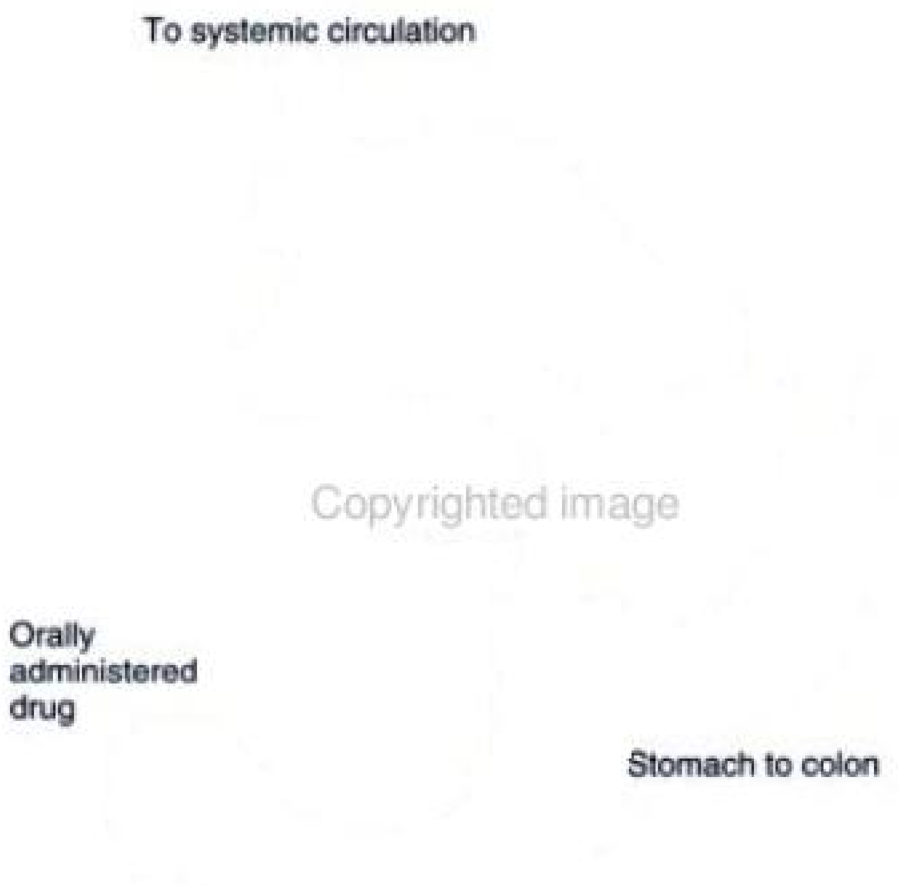

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Figure 1–5. First-pass metabolism occurs as drug absorbed from the gastrointestinal tract (from the stomach to the lower colon) enters the portal vein and flows to the liver. Once in the liver, drugs that are characterized by a high extraction are removed rapidly from the blood before entering systemic circulation. Plasma concentrations of such drugs may not reach therapeutic concentrations unless the dose is increased to compensate for first-pass metabolism. The amount of drug removed on the first pass from the liver differs among species and ages and according to the presence or absence of disease.

are administered either parenterally or in oral doses high enough to compensate for first-pass metabolism by the liver. Examples of drugs that undergo significant first-pass metabolism include selected cardiac drugs (e.g., propranolol, diltiazem in some species, hydralazine, nitroglycerin), diazepam, and opioid analgesics. The negative effects of first-pass metabolism on pharmacologic response may be reduced if the drug metabolites (e.g., propranolol and diazepam) are also pharmacologically active.

Obviously, the greater the extent of absorption of a drug, the greater the anticipated pharmacologic response to the drug. It is important to note, however, that pharmacologic response may vary even if bioavailabilities are equal because of differences in bioequivalence. A drug whose rate of absorption is slower may be completely absorbed (i.e., bioavailability is 100%), but the PDC may not reach the same magnitude or peak as another preparation or route. For example, although a drug may be completely absorbed from a slow-release preparation (e.g., slow-release theophylline oral preparations or reposital forms of intramuscular or subcutaneous penicillin preparations), a therapeutic concentration may never be reached because absorption occurs very slowly. The absorption rate constant, k_a, of a drug is the slope of the upswing of the PDC versus time curve after non-IV drug administration (see Fig. 1–3). Absorption half-life, derived from the k_a, is a clinically useful parameter that indicates the time necessary for 50% of a drug to be absorbed. At three drug absorption half-lives, 87.5% of a drug has been absorbed. Note that drug excretion begins as soon as drug is absorbed and distributed to organs of excretion. For noncompartmental models that describe the pharmacokinetics of a drug, the mean absorption time (MAT) is likely to be the parameter reported for assessing drug absorption from the site of administration.

Distribution

Once a drug reaches the systemic circulation, it may be distributed from the central (blood) compartment to peripheral tissues, including the site of drug action. The major factors that determine drug distribution to and from tissues include the lipid solubility of the drug and its ability to penetrate cell membranes; the degree to which the drug is bound to plasma or tissue proteins; and regional (organ) blood flow.

The amount of tissue to which a drug is distributed, often estimated by the *volume of distribution* (Vd) of the drug, directly influences PDC (Ritschel, 1992; Rowland, 1989). This theoretical volume is the volume to which a drug would have to be distributed (or the volume that would dilute the drug) if it were present throughout the body in the same concentration as that measured in the plasma. This parameter can be exemplified by adding 5 g of dextrose (the dose) to two beakers, each containing a different but unknown volume of water. Assume that the dextrose is allowed to distribute equally (reach equilibrium) in each beaker. The concentration of dextrose after equilibrium has been reached in beaker A is 5% (50 mg/mL or 5 g/100 mL), while the concentration in beaker B is 2.5% (25 mg/mL or 25 g/100 mL). The volume of water contained in beaker A (its Vd) must be 100 mL while that in beaker B is 200 mL. The Vd for a drug in an animal is measured in a similar manner: a known amount (dose) of drug is administered intravenously to ensure that all drug reaches systemic circulation (i.e., F = 100 %). The maximum PDC is determined after (distribution) equilibrium has been reached but before excretion has begun. Because the PDC cannot be measured immediately at time 0 (and thus before some excretion), the PDC at time 0 is often based on extrapolation of the PDC curve back to time 0 for drugs whose decline in PDC is described by one drug movement. The maximum concentration in such instances is referred to as C_0 (see Fig. 1–3) (Ritschel, 1992; Rowland, 1989). The Vd of a drug then can be calculated:

$$\mathrm{Vd} = \mathrm{Dose}/C_0$$

For drugs that follow a two or more compartment model, Vd is calculated from PDCs after distribution equilibrium is complete (B; Fig. 1–3, plot B), which is, in turn, determined by extrapolating the terminal component of the PDC versus time curve to the y axis. Alternatively, the volume of distribution at steady state (Vd_{ss}) can be calculated with models that are noncompartmental. Note that Vd can be determined only after IV administration because that is the only route by which 100% of the administered dose reaches systemic circulation (i.e., bioavailability is 100%). Occasionally scientific articles or drug package inserts report Vd_{ss} (Vd at steady state)/F or Vd/F. These values are of little clinical or scientific relevance unless the biovailability of the product or compound in question is known for the route being reported. If bioavailability is 100%, then Vd = Vd/F. If F is less than 100% (or <1) then Vd will be increased proportionately. Because dose is generally in milligrams per kilogram and C_0 is generally milligrams per milliliter (the same as grams per liter), Vd is generally reported as liters per kilogram.

The PDCs after administration of a fixed dose vary inversely with Vd. Volume of distribution differences among species and ages (pediatric vs. geriatric) can dramatically affect PDC after administration of a known dose. In addition, diseases associated with fluid retention or obesity are likely to increase the Vd of many drugs (and thus decrease PDC), whereas dehydration or weight loss is likely to decrease Vd and thus increase PDC. For example, if a patient were to receive intensive fluid therapy, the Vd of the patient might increase dramatically, causing a subsequent decrease in PDC. Volume of distribution also influences elimination half-life (Fig. 1–6).

Drug binding to proteins affects several determinants of drug movement, but particularly distribution (Craig, 1989) and thus Vd. Weakly acidic drugs tend to bind to albumin, whereas weakly basic drugs tend to bind to α_1-glycoproteins (Belpaire, 1987). Many drugs are also bound to tissue proteins. Proteins are water soluble and much larger than the drug. Plasma protein binding renders a drug more water soluble, thus facilitating its movement in circulation. The protein-bound drug cannot, however, be distributed from plasma into tissues or from tissues back to plasma. In addition, the protein-bound drug is not pharmacologically active, cannot be renally excreted, and, for many drugs, is more slowly metabolized by the liver. Drugs that are highly protein bound (>80%) may be more likely to be involved in adverse reactions early in the dosing regimen because displacement of only a small proportion of drug from the protein (i.e., due to competition with other protein-bound drugs or to hypoalbuminemia) can increase the total amount of free, active drug (Fig. 1–7) (Ritschel, 1992; Rowland, 1989). For example, displacement of only 1% of a drug that is 99% protein bound (e.g., nonsteroidal anti-inflammatories) can double the concentration of pharmacologically active drug. Clearance of these drugs often increases (see later discussion), however, and PDC eventually returns to normal as a new equilibrium is reached. Displacement from plasma proteins also increases Vd because the drug is more likely to enter tissues when freed. Because the drug is removed from the organs of elimination, the half-life of the drug also is likely to increase.

Highly protein-bound drugs do not distribute into tissues but remain in systemic circulation. Because the Vd of bound drug is small, such drugs may distribute to their total volume almost instantaneously. The PDC versus time line might present as a single-component, or a one-compartment, open model (open because drug leaves the system) because the decline in PDC reflects only excretion from the body. The Vd of drugs that are highly (>80%) bound to plasma proteins (e.g., albumin or α-glycoproteins) tends to be small (i.e., <0.1 L/kg), reflecting the plasma central compartment, which is about 5% of body weight. Note, however, that the Vd of the unbound portion of drug can be very high, depending on drug chemistry and tissue accumulation of the drug.

If a semipermeable membrane divided the beakers used to exemplify Vd into two compartments, distribution of the dextrose throughout each beaker would have taken longer. Drug concentrations in the beaker could not have been measured until a distribution equilibrium had been reached (i.e., the amount of drug passing through either side of the membrane was equal). The membrane may have not allowed equal distribution of the drug. Thus, both rate and extent of distribution could have been altered. The same scenario exists in an animal, but the semipermeable membrane is complex and may result in multiple compartments. For example, drugs that distribute to extracellular fluid (ECF) or to intracellular fluid (ICF; i.e., total body water [TBW]) generally take progressively longer to reach equilibrium. The PDC versus time line of such drugs may present as two components or as a two-compartment open model (see Fig. 1–3). The first component of the line declines due to both excretion and distribution; the second component declines due to excretion alone because a distri-

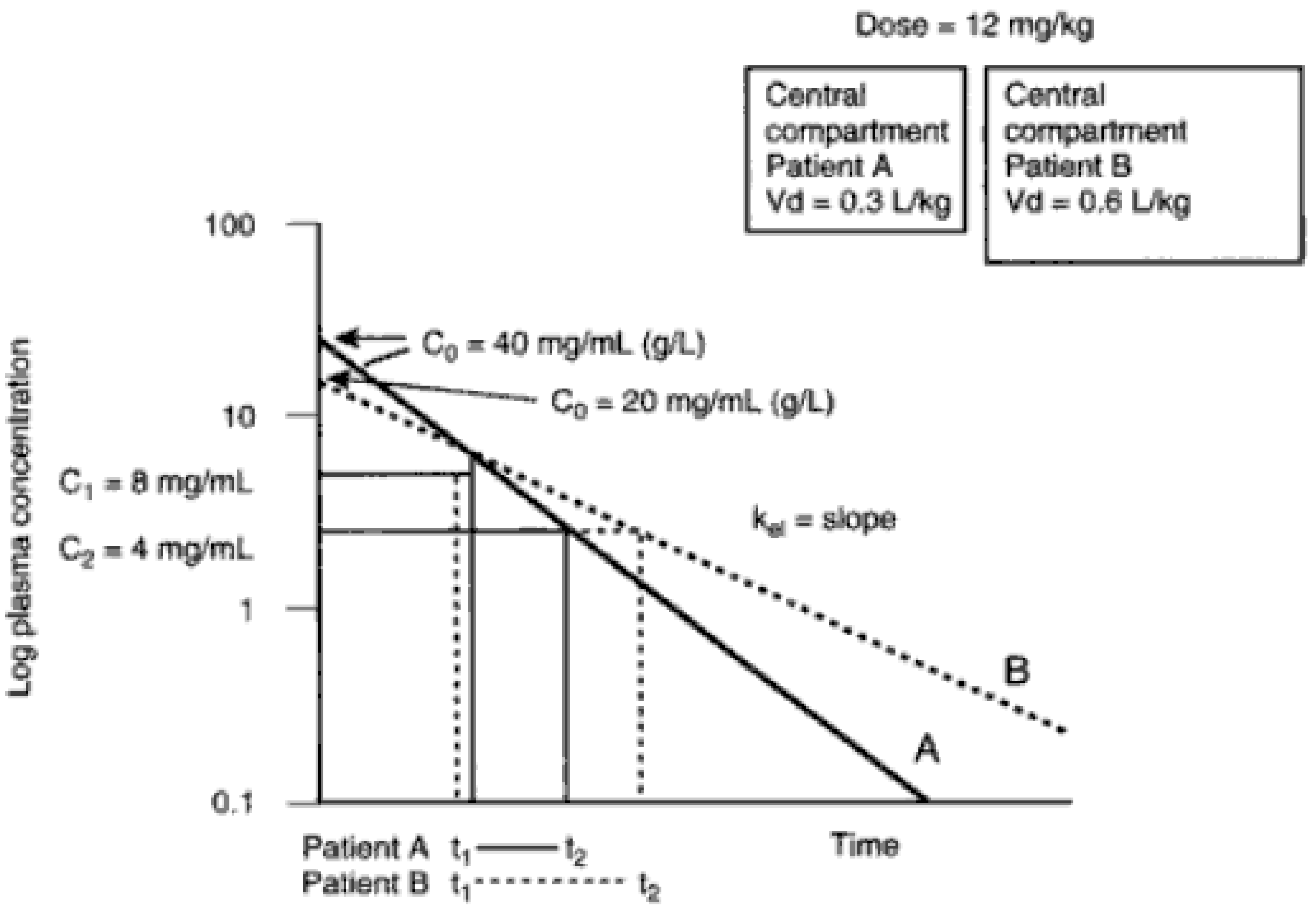

Figure 1–6. Changes in volume of distribution (Vd) impact both peak plasma drug concentration (PDC) (C_0) and the slope of the elimination (k_{el}) curve that determines elimination half-life. Plot A represents PDC versus time following administration of a dose of drug in an animal with a volume of distribution that is half of that represented in plot B. Note that the slope of the plasma elimination curves for the drug is flatter in the patient with the larger volume of distribution. This half-life also will be longer. Drug half-life in the two patients can be compared by comparing the time ($t_2 - t_1$) necessary for PDC in patient A to drop 50% (C_1 to C_2) with the time necessary for the same drop to happen in patient B.

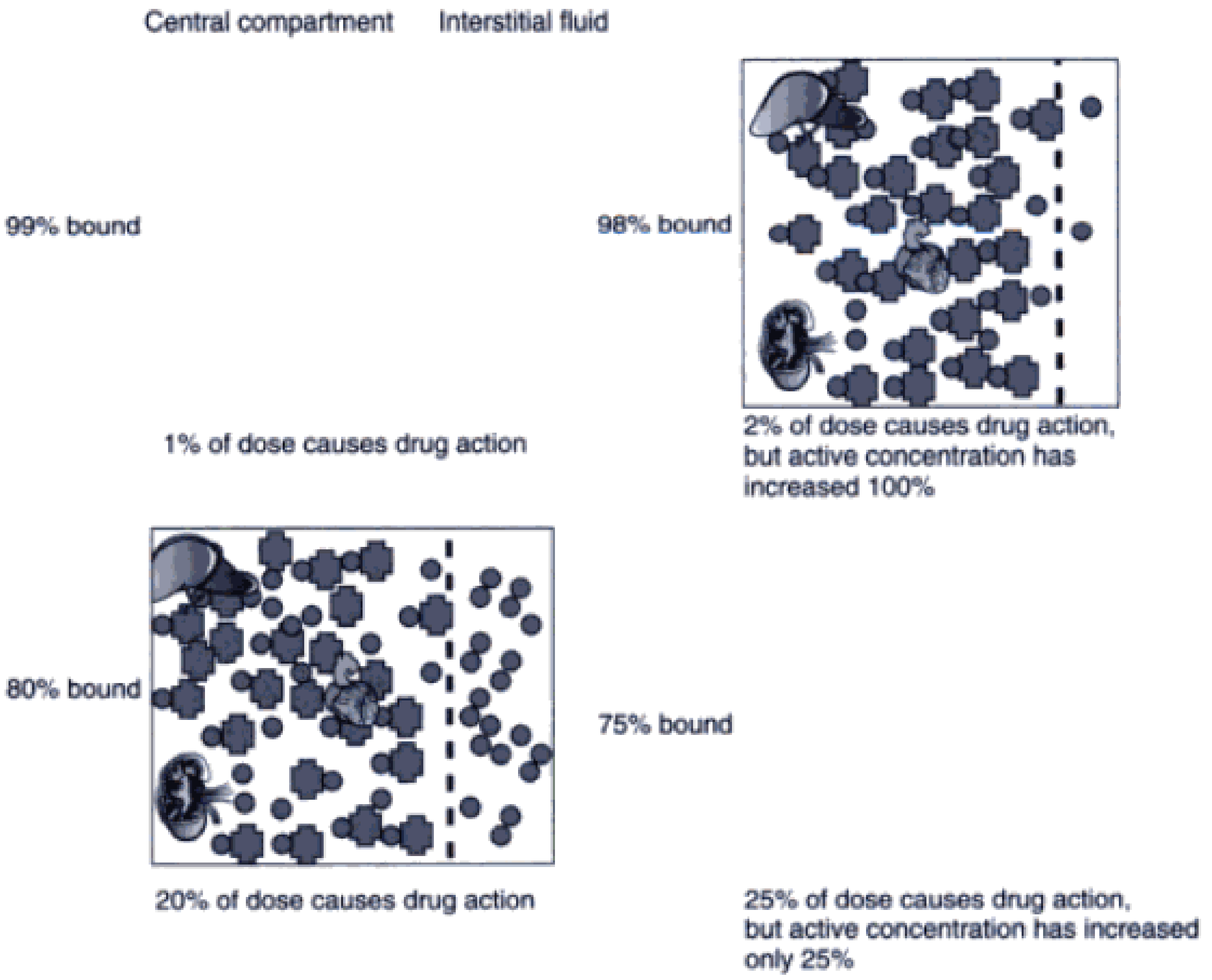
Central compartment
Interstitial fluid
99% bound
98% bound
1% of dose causes drug action
2% of dose causes drug action, but active concentration has increased 100%
80% bound
75% bound
20% of dose causes drug action
25% of dose causes drug action, but active concentration has increased only 25%

Figure 1–7. Displacement of drug from protein-binding sites becomes significant only if a drug is greater than 80% protein bound. Displacement of only 1% of a drug that is 99% protein bound doubles the pharmacologically active form of the drug (top two diagrams). For a drug that is 80% protein bound, however, 20% of the dose is responsible for pharmacologic actions. Displacement of 1% minimally impacts the concentration of active drug; displacement of 5% (from 20% to 25%) increases the amount of active drug by only 25% (5/25).

bution equilibrium has been reached (i.e., drug distributing from tissues into circulation equals drug distributing from circulation into tissues).

The rate at which a drug is distributed to tissues can be scientifically represented by the slope of the initial component or phase of the PDC versus time line following IV administration (Fig. 1–3, plot B). The excretion component of a two-compartment model must first be mathematically "stripped" or subtracted before the distribution slope or rate constant (often referred to as α) can be determined (see Fig. 1–3, plot B). The *distribution half-life*, derived from the first component of a fitted curve, measures the time necessary for 50% of distribution to be completed and offers a means for estimating the time that must elapse before drug distribution to tissues is complete and has reached equilibrium (Gibaldi, 1982, 1985; Martinez, 1998c). Clinically, this parameter becomes important because C_{max} will not be achieved in tissues until distribution has reached an equilibrium. If PDCs are being monitored in a patient, blood samples for peak drug concentrations should not be collected until distribution has reached an equilibrium. For many drugs, both absorption and distribution are complete within 1 to 2 hours after administration. If a drug is given orally, intramuscularly, or subcutaneously, the graphical representation of distribution may be "hidden" in the absorptive phase of drug movement.

Water-soluble drugs tend to be distributed to ECF and thus are often characterized by a Vd of 0.1 to 0.3 L/kg. Lipid-soluble drugs may cross cell membranes and thus distribute to ECF plus ICF (i.e., TBW); such drugs generally have a larger volume of distribution (>0.6 L/kg). Regardless of solubility (water or lipid), drugs that are not bound to plasma proteins are able to pass unimpeded through the fenestrated capillaries into extracellular fluid. At distribution equilibrium, drug concentrations in ECF are in equilibrium with that in plasma. The capillaries of selected organs, including the brain, cerebral spinal fluid, eye, testis, and prostate, are not, however, fenestrated (Bergan, 1981; LeFrock, 1984), and drugs must diffuse through the capillary endothelium in order to penetrate the target tissue. For treatment of such organs, lipid-soluble drugs are more likely to penetrate the endothelial barrier.

Drugs that are bound to tissues may take even longer to reach distribution equilibrium, and the PDC versus time curves may be composed of three or more components. The Vd of such a drug (e.g., digoxin in cardiac tissue and aminoglycosides in renal tubular cells) is often greater than 2 L/kg, which is greater than TBW. Although Vd is a useful parameter with which to predict the magnitude of distribution of a drug, it is only theoretical and does not confirm where (i.e., ECF, ICF, TBW, or binding to tissues) the drug has distributed.

The ability of a drug to penetrate cell membranes is an important consideration when therapeutic success depends on reaching intracelluar sites. Many bacterial infections are intracellular, and antibiotic selection might be based on drugs capable of reaching intracellular sites. For example, doxycycline rather than tetracycline may be the preferred treatment for ehrlichiosis.

Metabolism

The rate at which a drug is excreted from the body is the final determinant of PDC. Most drugs are eliminated by hepatic metabolism, renal excretion, or both (Ritschel, 1992; Rowland, 1989). Lipid-soluble drugs require conversion to a water-soluble form before they can be eliminated by the kidney. Such drugs usually are subjected to hepatic metabolism, which can occur in two phases (Fig. 1–8). Phase I metabolism chemically changes the drug so that it is (usually) more water soluble and more susceptible to phase II metabolism. Reactions include oxidation, hydrolysis, and reduction. The enzymes responsible for the majority of phase I metabolism are referred to as cytochrome P450 enzymes, a reference to their chemical structure (which contains an iron central core) and the wavelength at which they absorb light (450 nm). Experimentally, when the liver is subjected to homogenization and centrifugation processes, the smooth endoplasmic reticulum that contains the enzymes forms minute vesicles or microsomes; hence the term microsomal drug-metabolizing enzymes. The cytochrome P450 system is a large superfamily containing several families of enzymes (Schenkman 1982; Parkinson, 1996). Note that cytochrome P450 is not the only drug-metabolizing enzyme in the liver or body, and the liver is not the only source of phase I drug metabolizing enzymes. Other organs with substantial metabolic capacity attributable to cytochrome P450 or other enzymes include the lungs, skin, and kidney. Phase I metabolites are usually inactive (e.g., phenobarbital) but can be equally, more (i.e., a pro-drug such as enalapril), or less (e.g., diazepam) active or more toxic (e.g., acetaminophen [Mitchell, 1984]) than the parent compound.

Phase II metabolism, also known as *conjugation*, occurs when a large water-soluble molecule is chemically added to either the parent drug or a phase I metabolite. Glucuronidation is the most common phase II reaction. Addition of glutathione to a reactive metabolite is an important mechanism by which reactive metabolites can be scavenged before tissue damage occurs. Sulfonation and acetylation are less common phase II reactions. With rare exceptions, phase II metabolites are inactive. Acetylation occasionally results in formation of active metabolites (e.g., procainamide). Most drug metabolites are eliminated in the urine. Species differences in both phase I and phase II metabolism are well recognized (see Chapter 2).

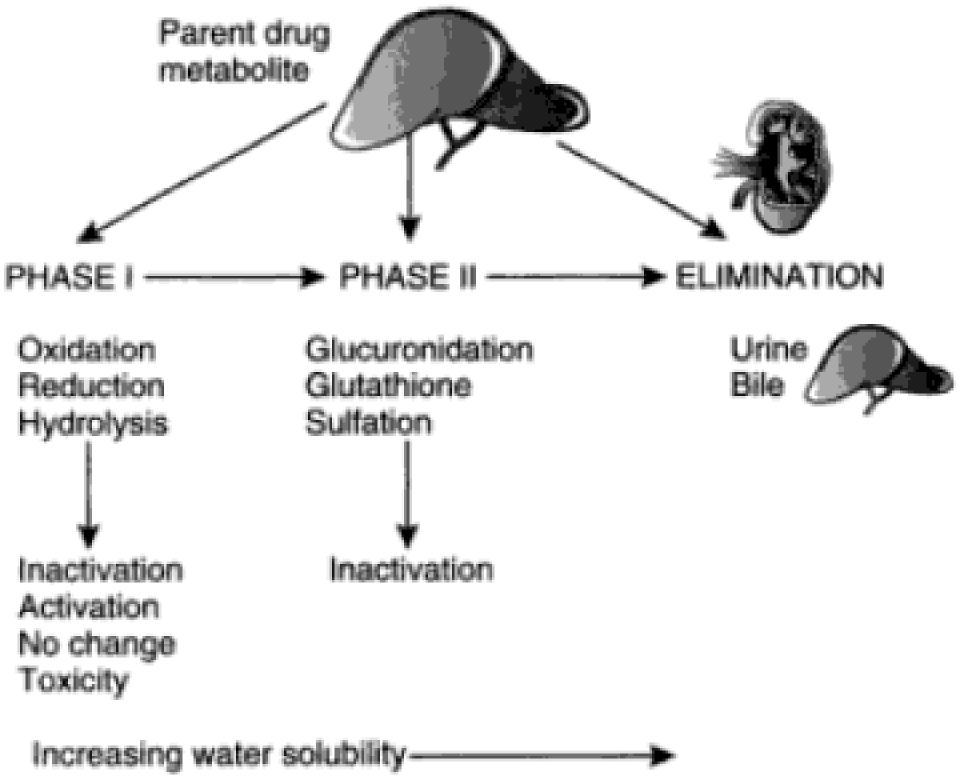

Figure 1–8. Hepatic metabolism can occur in one, two, or multiple phases. Phase I reactions are oxidative, most often accomplished by cytochrome P450 (hepatic microsomal) enzymes. Phase I metabolites may be subjected to either phase I or phase II metabolism. Phase I metabolites can be an important source of drug-induced toxicity. Phase II metabolism generally inactivates the drug. The rate and extent of both phases of metabolism vary among species, ages, and disease states.

Factors that can affect hepatic drug metabolism include the amount and activity of drug-metabolizing enzymes and, if the drug is characterized by a high extraction ratio (>70%, a "flow-limited drug"), hepatic blood flow. Changes in protein binding of highly bound drugs can also affect the rate of hepatic metabolism of drugs characterized by a low (<70%) extraction ratio. The greater the protein binding, the slower the rate of metabolism. Capacity-limited drugs are drugs with low extraction but highly protein bound. The rate of elimination of such drugs is inversely proportional to their degree of protein binding. For such drugs, decreasing protein binding results in an increase in the rate of metabolism. In contrast, protein binding does not impair the extraction of flow-limited drug. Disease, drug interactions, and species differences can have a profound impact on drug metabolism and thus on the duration of drug elimination.

Renal and Biliary Excretion

Renal excretion is the most important route of drug elimination for both parent drugs and their metabolites (Ritschel, 1992; Rowland, 1989; Somoygi, 1987; Bekersky, 1989) (Fig. 1–9). The elimination of water-soluble drugs (e.g., aminoglycosides and β-lactams) particularly depends on renal excretion. Host factors that determine renal excretion include glomerular blood flow, active tubular secretion, and tubular reabsorption. Each of the determinants of renal excretion can be influenced by renal blood flow. The kidney is also capable of metabolizing some drugs (e.g., imipenem), although this capacity is only occasionally of clinical importance.

Glomerular filtration is a passive process. Drugs enter the glomerulus by bulk flow, being excluded if too large (> 60,000 molecular weight) or if bound to large molecules such as albumin. In contrast, active transport of drugs in the proximal tubules is very efficient and rapid, and although insensitive to protein-binding, is susceptible to competition among drugs. Separate transport proteins exist for acid, basic, and neutral drugs. Probenecid has been used clinically to compete with and thus inhibit the renal excretion of expensive β-lactam antibiotics (e.g., imipenem), thus prolonging therapeutic PDC (see Fig. 1–9). Reabsorption of drugs from renal tubules into peritubular capillaries slows renal excretion. The extent to which a drug is reabsorbed depends on its lipid solubility and its ionization. Weakly acidic drugs are more likely to be reabsorbed in acidic urine but are trapped and excreted in alkaline urine. Urinary pH can be therapeutically altered such that the renal excretion rate of a drug can be modified. Note that for drugs renally excreted (e.g., amoxicillin), minimum inhibitory concentrations referring to PDCs are inappropriate guides to drug therapy of urinary bladder (but not renal) infections because drug concentrations achievable in the urine are much higher than those in the plasma. A drug can be concentrated in the urine up to 300-fold compared with plasma concentrations.

In contrast to renal excretion, biliary excretion is very

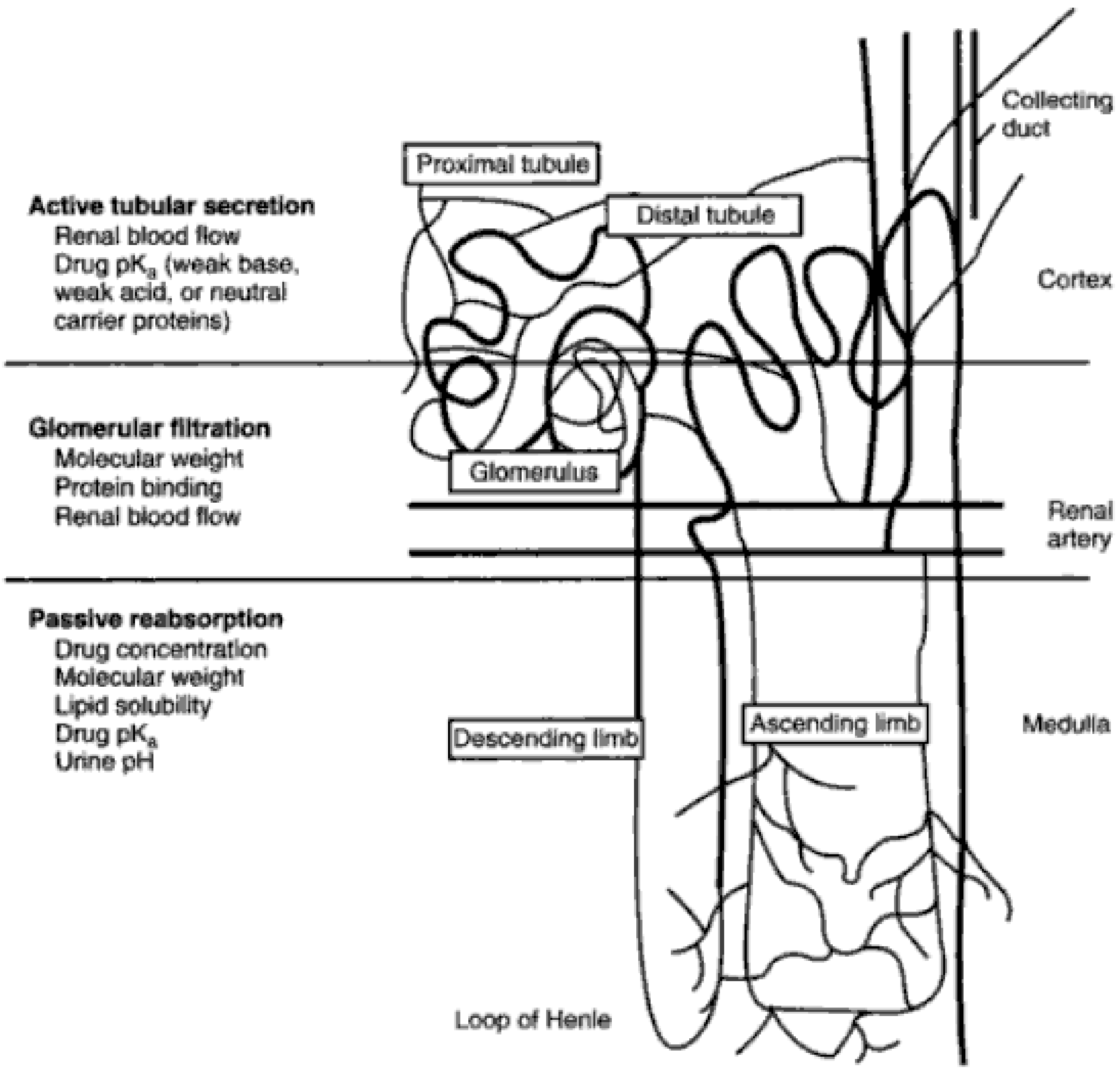

Figure 1–9. Renal excretion is the most common route of elimination of drugs and their metabolites. Three drug movements determine the rate of renal excretion. Active tubular secretion in the proximal tubule is a rapid process and is not limited by protein binding. Glomerular filtration is a passive process; protein-bound drugs cannot be filtered through the glomerulus. The rates of both active tubular secretion and glomerular filtration both depend on renal blood flow. Un-ionized drugs that are sufficiently lipid soluble may be passively resorbed. Because urine drug concentration increases, passive resorption should also increase the concentration.

slow and is much less clinically important. Drugs are eliminated in the bile by at least three active transport systems: one each for organic acids, organic bases, and organic neutral compounds. Characteristics that determine biliary excretion of drugs include chemical structure, polarity, and molecular weight, with the latter being one of the major determinants. Drugs excreted in the bile are in greater contact with the intestine and its flora compared with other drugs and are thus more likely to cause adverse reactions in the gastrointestinal tract. In addition, drugs excreted by this route may undergo enterohepatic circulation (Fig. 1–10). When excreted into the bile in the conjugated form, drugs cannot be reabsorbed from the intestine because of the large molecule weight. Bacterial degradation can, however, result in free, unconjugated drug that can then be reabsorbed back into systemic circulation. Enterohepatic circulation prolongs drug elimination half-life.

Elimination

The combined effects of renal and biliary excretion, as well as other routes of elimination not discussed (i.e., pulmonary, sweat) irreversibly remove drug from the body. The rate of drug elimination, k_{el} (also β or γ, depending on the number of linear components that compose the PDC vs. time curve), describes the fraction of drug in the body irreversibly eliminated per unit time (time^{-1}) (see Fig. 1–11) (Rowland, 1989; Ritschel, 1992; Martinez, 1998a, c). This rate is represented by the slope of the terminal component of a PDC versus time curve (the initial components, if present, generally represent both distribution and elimination).

Because k_{el} is a slope, it can be calculated from only two points on the PDC versus time curve, such as might be obtained from a peak and trough sample collected as part of therapeutic drug monitoring. The slope, or k_{el}, is simply the rise/run, or $C_1 - C_2/t_2 - t_1$, where C is the concentration of sample 1 or 2 and t is the time that samples 1 and 2 were collected (see Fig. 1–6). Because the PDC is plotted logarithmically, the actual equation becomes

$$\frac{\ln\left\{\frac{C_1}{C_2}\right\}}{t_2 - t_1}$$

For example, if gentamicin samples collected at 2 hours and 12 hours after an IV dose were 10.5 and 2.0 mg/mL, the k_{el} for gentamicin in this animal would be 0.17 h^{-1} The elimination half-life of a drug is the time necessary for half of the drug to be eliminated from the body (Fig. 1–11). It is derived from k_{el} ($t_{1/2} = 0.693/k_{el}$ (see Fig. 1–3) and is one of the most useful parameters for determining an appropriate dosing interval. It can also be derived from the plot of drug concentration (semilog) versus time curve (see Fig. 1–6). In the above example, the half-life of gentamicin in this patient is 4.2 hours. At one drug elimination half-life, 50% of the dose has been eliminated; by

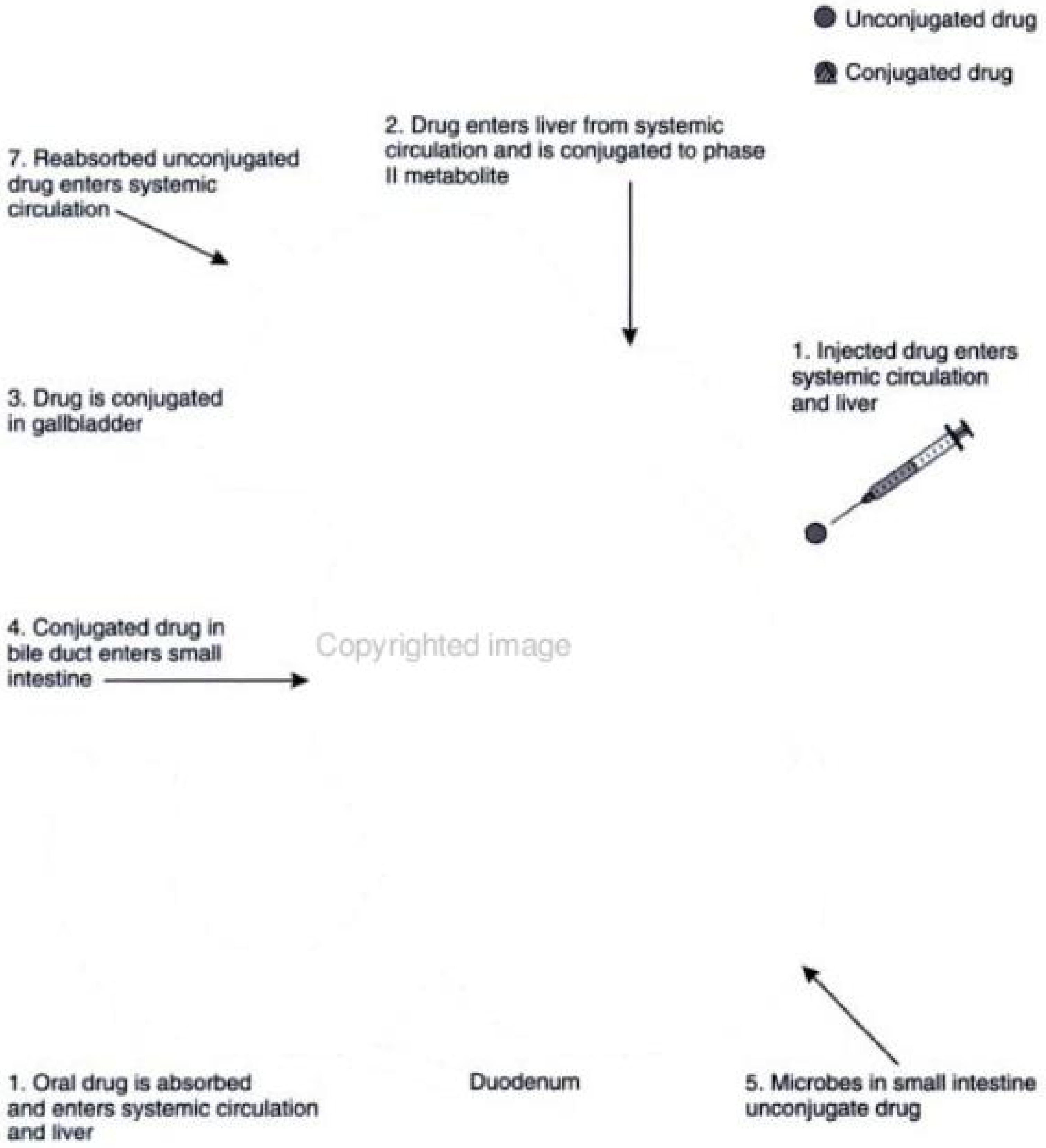
● Unconjugated drug
Conjugated drug
7. Reabsorbed unconjugated drug enters systemic circulation
2. Drug enters liver from systemic circulation and is conjugated to phase II metabolite
1. Injected drug enters systemic circulation and liver
3. Drug is conjugated in gallbladder
4. Conjugated drug in bile duct enters small intestine
1. Oral drug is absorbed and enters systemic circulation and liver
Duodenum
5. Microbes in small intestine unconjugate drug

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Figure 1–10. Enterohepatic circulation can prolong the elimination half-life of a drug. Following oral or parenteral administration, the drug is conjugated in the liver and eliminated in the bile. The drug travels from the duodenum to the lower small intestine and colon. Bacterial degradation results in deconjugation of the drug, which can then be reabsorbed.

five drug half-lives, more than 97% of the drug has been eliminated (see Fig. 1–11). For gentamicin in this patient, approximately 21 hours must elapse before most of the drug has been eliminated.

The importance of first order (constant fraction) versus zero order (constant amount; see Fig. 1–11) (Dayton, 1967) can be appreciated best in the context of the elimination rate constant. A k_{el} of 0.25 h^{-1} suggests that 25% of the drug remaining in an animal's body is eliminated each hour. A comparable zero-order rate (a constant amount) might be 25 mg each hour. Assume an animal has ingested several aspirin to the point that the PDC has surpassed the

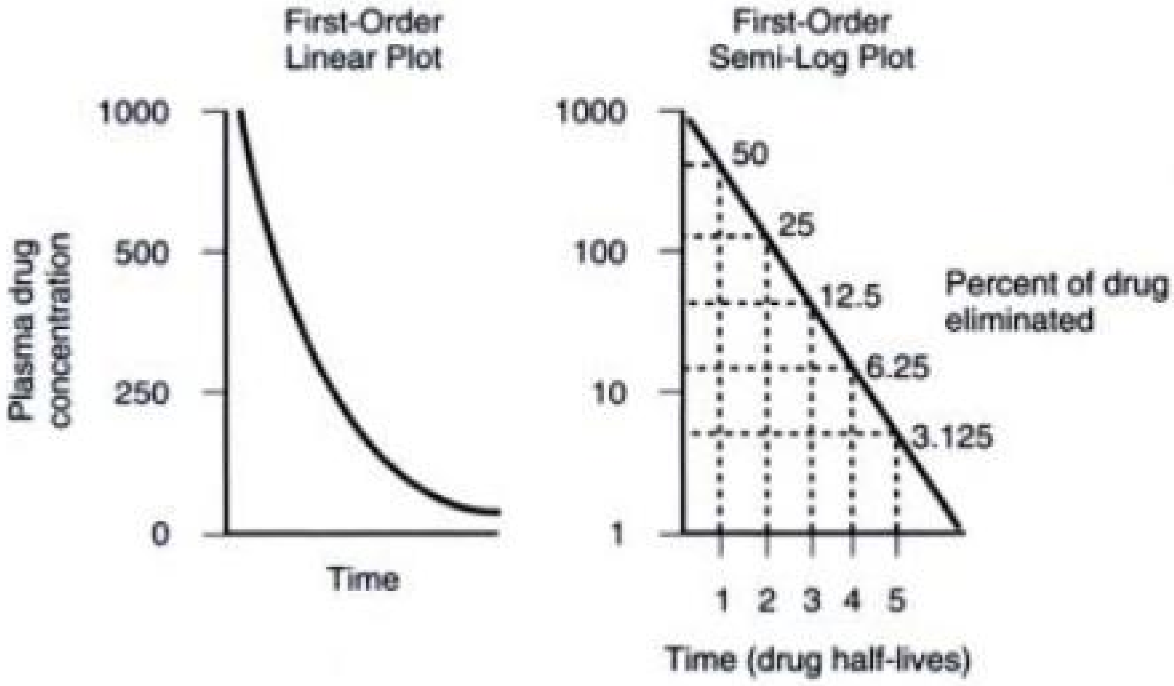

Figure 1–11. Drug elimination half-life can be derived from the plasma drug concentration versus time plot. Because most drugs are eliminated first order (a constant fraction is eliminated per unit time), the relationship between concentration and time is linear when plotted on semilogarithmic paper but curvilinear when plotted on linear paper. If a line is drawn between two points (such as might be obtained from a peak and trough concentration), the line can be extrapolated to the y axis. The half-life is the time that elapses as plasma drug concentration decreases by half.

therapeutic range of 100 to 500 mg/mL. With first-order elimination, by 8 hours (72 hours) in the dog, PDC essentially has reached the therapeutic range (500 → 250 and so on until 112 mg/mL is left by 8 hours). With zero-order elimination (25 mg eliminated per hour), 36 hours must elapse before 100 mg/mL is reached. Thus first-order elimination might be considered a protective mechanism to ensure rapid elimination of potentially toxic substances. In addition to dosing interval, elimination half-life determines time to steady state. Together with the dosing interval, the elimination half-life also determines the amount of fluctuation in PDC during a dosing interval and the degree of drug accumulation as steady-state equilibrium is reached (see discussion of accumulation later in this chapter). Studies using noncompartmental models to pharmacokinetically describe drug movements report mean residence time (MRT), which is the average time a molecule is in the body (or the time necessary for 63.2% of a drug to be eliminated).

Clearance is a parameter often used to assess the excretion capacity and thus physical well being of an organ. Plasma clearance (Cl) is the volume of plasma irreversibly cleared of the drug per unit time and represents the sum total of organ clearance (Fig. 1–12) (Ritschel, 1992; Rowland, 1989; Martinez, 1998c, d). Note that it differs from elimination because it is a volume per unit time, not a rate constant. If the drug is cleared exclusively by one organ (e.g., renal clearance of aminoglycosides or hepatic clearance of caffeine), then plasma Cl also represents clearance of the specific organ and can be used to evaluate the function of the organ. The volume of blood cleared per unit time by an organ is independent of PDC. The same volume of blood is irreversibly cleared of drug by an organ regardless of how much drug is in the blood (unless PDCs are so high that organs of clearance, such as the liver, become saturated). The Cl of a drug represents the fraction (k_{el}) of the Vd of a drug that is cleared per unit time. Thus, if the Vd and k_{el} (or half-life) of a drug are known, the Cl of the drug can also be determined:

$$Cl = Vd \cdot k_{el}$$

Note that Cl can be determined only after IV administration of a drug (unless F is known) because Vd can be measured only if bioavailability is known to be 100%.

Although clearance is the reason that PDC ultimately declines (thus is physiologically independent of any other factor), pharmacokinetically it is obtained or calculated from Vd and k_{el} (or half-life). Practically, it is not a useful parameter in the design of dosing regimens. In contrast, although half-life is a clinically useful estimate of how long a drug stays in the body physiologically, it is a "hybrid" parameter in that it is impacted by both distribution and clearance. Yet, pharmacokinetically, half-life is the "pure" parameter because it is measured directly from the PDC versus time curve. Obviously, the more rapidly a drug is cleared by an organ, the shorter the drug half-life. If a drug is distributed to a large tissue volume, however, the organs of clearance cannot access the drug, and the rate of elimination decreases. Thus, drug elimination half-life changes directly and proportionately with the volume of distribution of a drug, but inversely (and proportionately) with the clearance of the drug.

The clinical significance of these relationships might be exemplified in a patient who has become dehydrated as a result of uncompensated chronic renal disease. As tissue volume contracts with dehydration, the volume of distribution decreases. Although PDC (and the risk of toxicity) increases, more drug is in each milliliter of blood, and thus more drug is cleared per unit time. If all else remains normal, drug half-life decreases. If renal function is significantly compromised and the patient is not yet dehydrated (and the drug is eliminated by the kidney), however, clearance decreases (a smaller volume of drug goes through the organs of clearance), and drug elimination half-life would decrease if all else remains normal. In the patient with both volume contraction and compromised renal function, drug half-life may not change even though renal function may be very impaired. With volume replacement (i.e., fluid therapy), drug elimination half-life would increase compared with the normal amount.

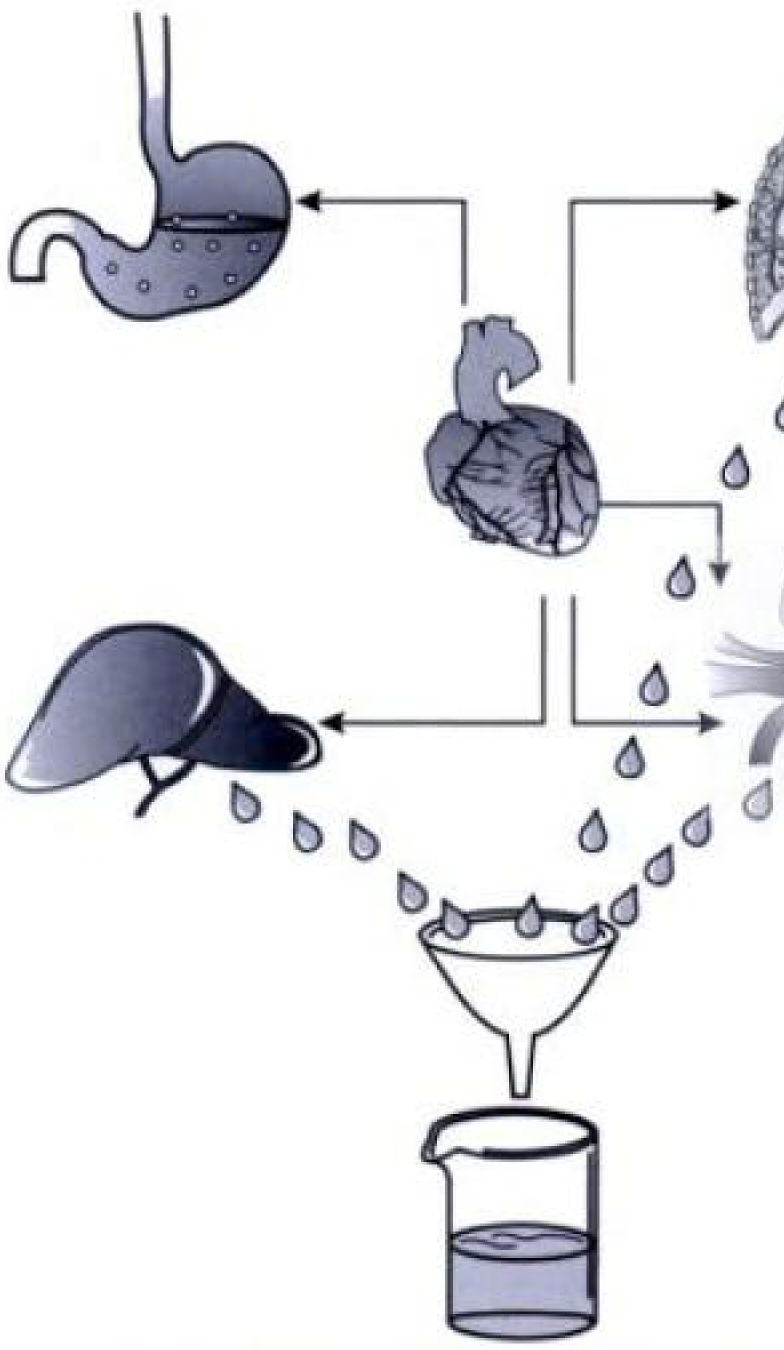

Figure 1–12. The clearance of drug from the body (plasma) is the sum total from each of the organs of clearance. Several organs not shown are also capable of drug clearance, most notably the skin.

FIXED DOSING REGIMENS

Dose

A fixed dosing regimen is composed of a dose and an interval (or frequency). The dose necessary to achieve a specified target PDC (e.g., C_{max} for many antimicrobials) depends on the volume of tissue that will dilute the dose administered, estimated by Vd (Ritschel, 1992; Rowland, 1989):

$$\text{Dose} = [C_{max}][\text{Vd}]$$

The dose of drug must be increased or decreased proportionately with changes in Vd in order to achieve the same target PDC (see Fig. 1–6). Often the dose is not intended to reach C_{max}, but rather C_{min} (i.e., phenobarbital) or midway between the two extremes of the therapeutic range. The concentration within a therapeutic range that is selected as the target depends on the drug efficacy and safety. The Vd of a drug is the sole determinant of PDC for IV administered drugs that do not accumulate. For drugs that do accumulate (see later), the initial dose of the drug must also take into account the magnitude of accumulation, which in turn depends on the elimination half-life of the drug in relation to the dosing interval. For oral drugs, bioavailability also must be considered: Dose = [Cmax] [Vd]/F.

Interval

The frequency of dosing, or the dosing *interval*, is determined by the time (T_{max}) it takes for maximum PDC (C_{max}) to drop to a point below which the desired response no longer occurs, C_{min} (Fig. 1–13). Thus, T_{max} depends on the amount of fluctuation in PDC desired during the dosing interval and the elimination rate constant (k_{el}). If C_{min} for a drug is close to half of C_{max}, then approximately one drug half-life (i.e., $T_{max} = t_{1/2}$) can elapse before the next dose must be administered. A more appropriate interval can be calculated with k_{el} if C_{min} does not approximate half of C_{max}:

$$T_{max} = \frac{\ln\left\{\frac{C_{max}}{C_{min}}\right\}}{k_{el}}$$

The longer the elimination half-life of a drug, the longer the interval (or T_{max}) can be between doses.

Frequently, to effect a pharmacologic response or to maintain owner compliance, clinicians are tempted to modify the recommended dosing interval. Yet decreasing a dosing interval is of no benefit for drugs whose half-life is long. For example, an 8-hour dosing interval for phenobarbital (or primidone; drug half-life 50 to 100 hours) offers no advantage to a 12-hour interval because very little drug is eliminated during the 12-hour period between doses. An exception is made if induction of drug-metabolizing enzymes by phenobarbital has decreased drug half-life (see Chapter 2). In contrast, prolonging a dosing interval for convenience may be dangerous for drugs with a short half-life (e.g., many antibiotics). For drugs with short half-lives, prolonging the dosing interval from every 8 hours to every 12 hours may be accompanied by a dramatic decrease in PDC, probably below C_{min} (Fig. 1–13*B*). Note, however, that some drugs are effective even though PDCs are essentially nondetectable. Examples include antimicrobials that exhibit a postantibiotic effect (e.g., aminoglycosides), drugs that accumulate in tissues (e.g., omeprazole), drugs such as diazepam whose metabolites are active (some with drug half-lives longer than the parent compound), and drugs that inactivate chemicals or destroy receptors that must be

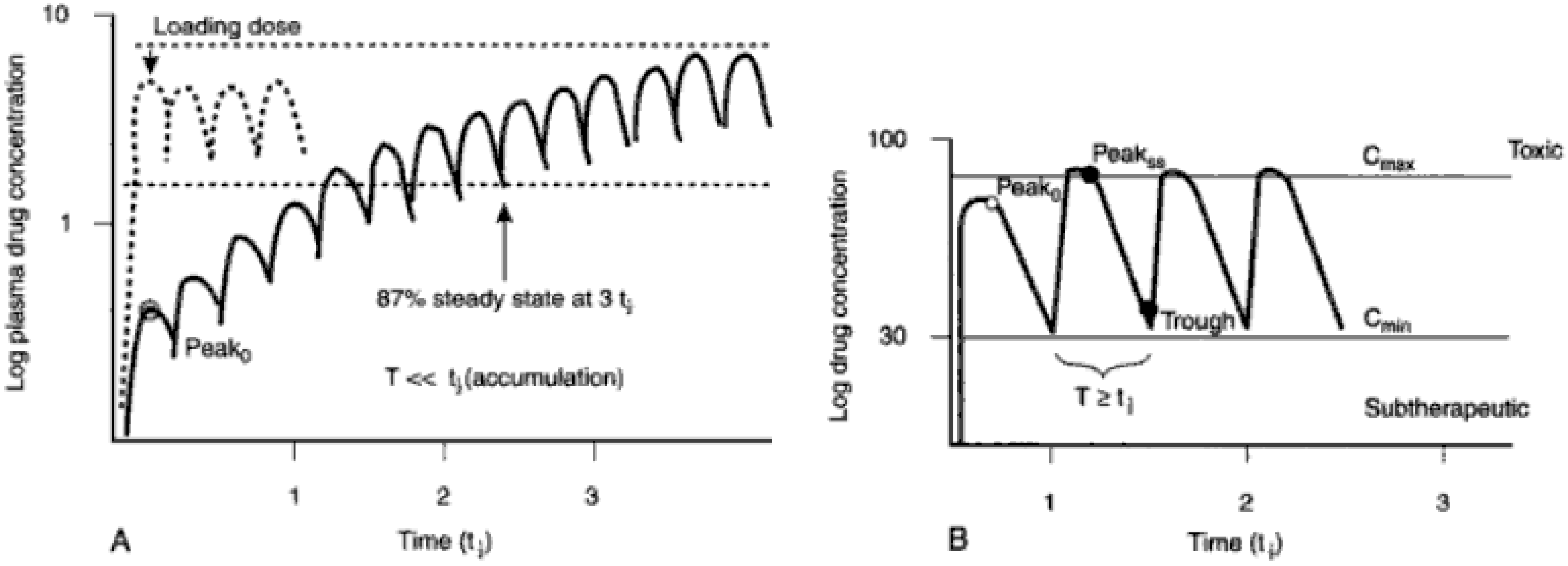

Figure 1–13. Plasma drug concentration versus time curves following multiple extravascular dosing. The therapeutic range of a drug is defined by a maximum concentration (C_{max}) above which toxicity is more likely and a minimum concentration (C_{min}) below which therapeutic failure is more likely. The amount of accumulation determines the drug concentration at steady state. The relationship between dosing interval (T) and drug half-life ($t_{1/2}$) determines the amount of a drug that will accumulate. A drug administered at an interval shorter than its half-life *(A)* will accumulate because most of the drug is still in the body by the next dose. Steady state occurs at five drug half-lives, when the amount of drug eliminated during a dosing interval equals the amount of the dose reaching systemic circulation. If a rapid therapeutic response is desired, a loading dose can be given. Note, however, that steady state has not been reached and PDC may increase or decrease if the maintenance dose is not correct. The magnitude of accumulation (peak concentrations following the first dose after the dose at steady state) depends on how much longer the elimination half-life is than the dosing interval. When monitoring is done for such drugs, generally a single sample collected at any time during the dosing interval is sufficient to reflect the whole dosing interval. A drug whose dosing interval is longer than its half-life *(B)* is less likely to accumulate because most of the drug will be eliminated during a dosing interval. The longer the dosing interval compared with the half-life, the less the drug will accumulate. Monitoring of such drugs ideally includes both a peak and trough sample from which elimination half-life can be calculated.

resynthesized before the physiologic effect resolves (e.g., antiprostaglandins). These drugs need not be given every half-life (often 2 hours or less) in order to remain effective. Half-life also determines the time that must elapse before a substantial amount of drug has been eliminated in the case of overdose (see Fig. 1–11). Although five drug half-lives must elapse before 97% of a drug is eliminated (see Fig. 1–11), loss of pharmacologic or toxic effect may be evident after only one or two half-lives have elapsed.

Drug half-lives can be as short as 2 minutes or less (e.g., epinephrine and dobutamine) or as long as several weeks (e.g., potassium bromide). Drugs with half-lives that are too short for convenient dosing are given either as constant IV infusion (e.g., lidocaine) or as a slow-release preparation (e.g., benzathine penicillin). Although the elimination half-life of the drug does not vary for these slow-release preparations, the absorption of the drug is much slower. The intent, although not always successful, is to maintain constant therapeutic concentrations by ensuring continuous addition or input of drug into plasma. Note, however, that absorption may be so slow that therapeutic concentrations are never reached. Many oral drugs are prepared as slow-release or continuous-release preparations (e.g., quinidine, theophylline). These preparations have, however, been formulated for humans, and the release kinetics may vary substantially in animals. For many of these drugs, effective PDC may not be reached.

Accumulation

For drugs with very long half-lives, dosing intervals are correspondingly prolonged. A dosing interval that is too long is, however, also often inconvenient. In addition, for many drugs, the therapeutic range is very narrow, and fluctuation of PDC during the dosing interval must be minimized. In both situations, the recommended dosing interval is often shorter than the drug elimination half-life. When each subsequent dose of drug is administered at an interval (T) that is much shorter than the drug half-life, most of the previous dose is still in the body and the drug begins to accumulate with multiple doses (Fig. 1–13*A*) (Ritschel, 1992; Rowland, 1989). Eventually, a steady state is reached for the drug such that the amount of drug administered with each dose equals the amount eliminated during the dosing interval. As with drug elimination, approximately five drug half-lives must elapse following a fixed dosing regimen before steady state is reached. Steady state is a relevant issue only for drugs that accumulate, that is, the drug (e.g., phenobarbital, potassium bromide, digoxin) is administered at a dosing interval that is shorter than the drug elimination half-life.

The amount that a drug will accumulate as steady-state PDCs are reached depends on the relationship between the drug elimination half-life and the dosing interval. The greater the difference between the two, the more the accumulation. The amount of accumulation can be approximated based on the relationship between the dosing interval (T) and the elimination half-life (Table 1–1). If the elimination half-life is equal to the dosing interval, the drug will accumulate twofold.

Table 1–1. Rate of Drug Accumulation Based on the Length of the Dosing Interval (T) Compared with Elimination Half-Life ($t_{\frac{1}{2}}$)

Accumulation*	Dosing Interval (Hours)	Elimination Half-Life (Hours)	T:$t_{\frac{1}{2}}$ Ratio
6.2	6	24	0.25
4.8	8	24	0.33
3.4	12	24	0.5
2	24	24	1
1.3	48	24	2
1.14	72	24	3
1.0	96	24	4

*Accumulation is the ratio of peak PDC following the dose at steady state compared with that following the first dose ($Cmax_{ss}$: $Cmax_{first\ dose}$).

The relationship between elimination half-life and dosing interval also determines the amount that PDC may fluctuate during a dosing interval. The larger the magnitude of elimination half-life compared with the dosing interval, the smaller the fluctuation in PDC during a dosing interval. For drugs administered at an interval equal to the elimination half-life, PDC will fluctuate twofold between doses. For example, if the elimination half-life of phenobarbital in a patient is 24 hours and the dosing interval is 24 hours, PDC at steady state accumulated twofold (i.e., by twice what it was after the first dose), and PDC will fluctuate between doses at steady state by 50%. Bromide and clorazepate (a benzodiazepine anticonvulsant) are extreme examples. The elimination half-life of bromide is 24 days, and the dosing interval is 1 day. At steady state, bromide concentrations will be over 25-fold what they were after the first dose. Likewise, during a 24-hour dosing interval, fluctuations in PDC will be so small that they likely will not be detectable. At the other end of the spectrum, clorazepate has an elimination half-life of less than 4 hours, but it might be administered every 12 hours. Because 87% of the drug is eliminated during each dosing interval, there is little drug accumulation. During a dosing interval, drug concentrations may become negligible (just before the next dose).

Clinically, drugs that accumulate present problems that are not encountered with drugs administered at an interval that precludes accumulation. Maximum therapeutic efficacy is not realized until steady-state concentrations are reached, which may be an unacceptable time for some patients (e.g., epileptics receiving potassium bromide [KBr]) (see Fig. 1–13). In such situations, a loading dose (i.e., 450 mg/kg KBr) can be administered. This single dose, based on the Vd of the drug (0.3 L/kg for KBr) and the target concentration (usually between C_{max} and C_{min}), is intended to achieve therapeutic concentrations with the first dose (assuming 100% bioavailability, it would be 1 to 1.5 mg/mL for KBr). The daily maintenance dose (e.g., 20 to 40 mg/kg for KBr) is administered after the recommended dosing interval has elapsed after administration of the loading dose. If the maintenance dose is not appropriate, PDC achieved after the loading dose may increase or decrease as steady state is reached. A disadvantage that may preclude administration of a loading dose is that the body is not allowed to gradually adapt to the drug.

For drugs that accumulate, the contribution of a single maintenance dose of drug to the total amount of drug in the patient's body at steady state can be considerably small, particularly if the dosing interval is much smaller than the drug elimination half-life (e.g., phenobarbital or KBr). If a pet owner fails to administer a dose of such a drug, the PDC is not likely to decrease below C_{min} and the patient is not likely to react adversely due to therapeutic failure (i.e., subtherapeutic concentrations). A double dose can be given at the next interval. Similarly, if the patient fails to respond to the drug because the PDC is inadequate, administration of a single "extra" dose is not likely to be beneficial because the PDC is not likely to change much. Rather, a (smaller) loading dose must be administered, or the maintenance dose will need to be increased and a new steady state reached at five drug half-lives.

Extrapolation of dosing regimens for drugs that accumulate is more difficult than for drugs with a short half-life. For the latter, the dose (for an IV drug) for multiple dosing depends only on Vd, which is a parameter that tends to be more similar among species. For drugs that accumulate, the dose (assuming multiple doses) must take into account both Vd and elimination half-life. Elimination half-life is more likely to vary among species, particularly if hepatic metabolism is important to drug elimination (i.e., lipid-soluble drugs).

Dosing Based on Body Surface Area
(Price, 1998)

The identification of a formula that predicted physiologic processes more accurately than body weight in children led to the use of body surface area (BSA) as a basis for dose selection of drugs characterized by a narrow therapeutic index. The formula is based on the assumption that rates of various physiologic functions, including those responsible for drug disposition, vary with body size (Price 1998). The formula $BSA = 10 \cdot W^{2/3}$ is based on the geometric relationship between BSA and volume, which, in turn, is addressed as body weight adjusted for mass. Because the relationship between body weight and volume is not constant, the equation is normalized for differences in body shape among species by the addition of the shape constant K: $BSA = K \cdot 10 \cdot W^{2/3}$. The formula is most commonly applied to designing dosing regimens for toxic yet therapeutic drugs, most notably cancer chemotherapeutic drugs, with the supposition that large breed dogs would benefit most (thus avoiding the relative overdosing they received compared with smaller dogs). However, recent recognition that when dosed based on BSA smaller dogs appear to react more adversely to cancer chemotherapeutic drugs than larger dogs has caused re-examination of the appropriateness of the generalized use of BSA to design dosing regimens for selected chemotherapeutic agents. Several observations made by Price and associates help support the need to re-examine the application of the method to all animals. First, studies have suggested that the mass exponent used to correct weight (2/3 or 0.67) is not correct. Other studies have shown that the exponent may vary as a function of age. This and other factors suggest that a range of mass exponents be applied to animals within the same species. Second, and more problematic but more obvious, is the variability in shape among animals within the same species. Although studies have shown that the allometric scaling of doses does help normalize doses among species, normalization using the same shape constant (K) within species has not been documented. Although a single K may be appropriate for the domestic cat, marked differences should be expected for the domesticated dog. Indeed, previous literature reveals that a number of shape constants have been used in dogs, ranging from 9.9 to 12.3 (Appendix 2), with the smaller value being applied to smaller or more compact dogs.

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2 Factors Affecting Drug Disposition and Extrapolation of Dosing Regimens

Dawn Merton Boothe

INTRODUCTION
PHARMACOLOGIC FACTORS
Pharmaceutical Drug Interactions
  Intravenous Preparations
  Oral Preparations
  Topical Preparations
Pharmacokinetic Drug Interactions
  Absorption
  Distribution
  Metabolism
  Excretion
Pharmacodynamic Drug Interactions
PATHOLOGIC FACTORS
Renal Disease
Hepatic Disease
Cardiac Disease
Thyroid and Other Diseases
PHYSIOLOGIC FACTORS
Age-Induced Differences
  Drug Disposition in the Geriatric Animal
  Drug Disposition in the Pediatric Animal
  Specific Drug Therapy for the Pediatric Patient
  Pregnancy and Lactation
Roles of Species and Breed Differences in Drug Disposition
  Absorption
  Distribution
  Metabolism
  Renal Excretion
Role of Species Differences in Target Tissues
  Breed Differences
  Miscellaneous
RECOMMENDATIONS REGARDING EXTRAPOLATION OF DOSING REGIMENS
Drug Information Sources
Water-Soluble Drugs
Lipid-Soluble Drugs
All Drugs
Compounding

INTRODUCTION

Ideally, fixed dosing regimens are based on scientific studies performed with the drug of interest in the target species. Often, however, the doses used in small animals are extrapolated from other species, especially humans, and are not based on scientific studies. Even with scientifically based studies intended to determine appropriate dosing regimens, the sample numbers studied are often too small to represent the target population. In addition, animals studied are generally healthy, yet animals treated with the drug often are not. Many factors in the individual patient can alter plasma drug concentrations (PDCs), and thus the likelihood of therapeutic failure, regardless of whether or not the dose is scientifically based. Some of these factors can be taken into account by modification of the dosing regimen. These factors include pharmacologic factors resulting from administration of the drug alone or in combination with other drugs (Table 2–1); pathologic factors, particularly cardiac, renal, or hepatic disease; and physiologic factors such as species and age.

PHARMACOLOGIC FACTORS

Drug interactions occur whenever the action of one drug is modified by the presence of another, concurrently administered drug. The incidence of interaction increases with the number of drugs included in the preparation and with the duration of treatment (Griffin and D'Arcy, 1979). Drug interactions may occur before or after the drug is absorbed. Although not necessarily a drug interaction, the route of administration can also influence both drug disposition and the type of drug interaction.

Pharmaceutical Drug Interactions

Pharmaceutical drug interactions occur before the drug is absorbed and may occur before administration. Interactions can occur between two drugs or between a drug and a carrier (solvent), a receptacle (including intravenous [IV] tubing), or the environment in which it is administered (e.g., gastric environment) (Ansel, 1976). In human medicine, pharmaceutical interactions most frequently result from the addition of drugs to IV fluid preparations. In veterinary medicine, they are most likely to occur in the critical care environment, where IV administration and multiple drug administration are common or following inappropriate compounding of drugs. Drug incompatibilities can change the chemical or physical nature of a drug. Incompatible reactions can reflect degradation due to changes in pH, binding by drugs with different charges, or other molecular interactions; changes in temperature; or exposure to ultraviolet radiation (Papich, 1995).

Intravenous Preparations

Drugs that are unstable generally have a short shelf life when in solution. Reconstituted parenteral solutions should always be labeled with the new expiration date and used with strict adherence to the product label instructions after reconstitution. If directed by the label, refrigeration or freezing can prolong the shelf life. It is risky, however, to assume that cold storage will prolong the shelf life of the drug unless efficacy has been documented at the intended conditions. Freezing can increase the degradation (e.g.,

Table 2–1. Examples of Factors That Affect Drug Disposition

- Pharmacologic factors
  - Pharmaceutical interactions
    - Therapeutical inequivalence
    - Direct drug-drug interactions
    - Drug-diet interactions
  - Pharmacokinetic interactions
  - Pharmacodynamic interactions
- Pathologic conditions modifying drug action
  - Gastrointestinal disease
  - Hepatic disease
  - Renal disease
  - Cardiovascular disease
  - Pulmonary disease
  - Neurologic disease
  - Metabolic disease
  - Drug protein binding
- Physiologic factors
  - Route of administration
  - Species variations
  - Genetic (breed) factors
  - Age
  - Sex
  - Body weight and surface area
  - Pregnancy and lactation
  - Diet and nutrition
  - Temperament
  - Environment
  - Circadian rhythms

ampicillin), crystallization (e.g., heparin, dobutamine, furosemide), or precipitation (e.g. insulin) of drugs. Refreezing of a previously frozen and defrosted solution increases the risk of efficacy loss. The proper reconstituting fluid should be used to avoid inactivation of drugs. For example, amphotericin B should be diluted only with 5% dextrose because precipitates will form otherwise; whole blood or packed red blood cells should be diluted only with 0.9% saline to avoid damage to infused cells (Table 2–2).

Changing the pH of a solution by improperly diluting it or mixing it with another drug can be risky. The release of some insulins is pH dependent. Diluting insulin with a solution other than that provided by the manufacturer may change the pH and thus the rate of insulin release. The pH of a solution may be needed to keep the active drug dissolved or stable; changing the pH may result in precipitation or loss of stability. For example, acid-labile drugs (e.g., penicillins) can be destroyed in a low pH solution. Drugs prepared as an acid salt (e.g., lidocaine hydrogen chloride) or in acidic solutions (i.e., sodium heparin) should not be combined with alkaline solutions (i.e., sodium bicarbonate).

Drugs can bind to and inactivate one another, often due to ionic attractions. Calcium in solutions causes precipitation when combined with solutions containing carbonates (e.g., sodium bicarbonate). Heparin is incompatible with several drugs, such as aminoglycoside and β-lactam antibiotics. Thus, whenever possible, saline rather than heparin should be used to maintain patency of catheters through which drugs are administered. When present in sufficiently high concentrations, penicillins inactivate aminoglycosides. In fact, ticarcillin can be used therapeutically to bind gentamicin in cases of overdose. Although plasma concentrations after therapeutic dosing of either drug probably do not achieve concentrations necessary to inactivate aminoglycosides, in the critical care situation, and as a once daily dosing regimen of aminoglycosides becomes more generally acceptable, the risk of aminoglycoside (or a fluorinated quinolone) antibiotic inactivation by a penicillin may become greater.

Often, a pharmaceutical drug interaction involving IV solutions can be detected by a visual change in the appearance of the drugs. Discoloration, cloudiness, and formation of precipitate generally are indications of an interaction, and with some exceptions use of the drug should be reconsidered. Not all interactions will, however, result in a physical change of the appearance. Likewise, the change in physical appearance of a drug combination does not necessarily indicate that the activity of the drug has been changed. For example, diazepam has been mixed with other preanesthetics with no observable change in drug efficacy, despite a cloudy discoloration. Whereas a pink discoloration of dopamine indicates inactivation, discoloration of dobutamine does not preclude efficacy if the drug is used within 24 hours. Slight yellow discoloration of procainamide is acceptable; dark discoloration indicates a loss of efficacy.

Several drugs can bind to receptacles. For example, lipid-soluble drugs (e.g., diazepam) can bind to plastic containers; insulin binds to selected glasses and to many plastics, including polyethylene and polyvinyl; aminoglycosides bind to glass. Binding to catheters and IV lines can be minimized by flushing each new system with a sufficient volume of solution (50 mL) before drug administration. Drugs packaged in brown bottles (e.g., diazepam and furosemide) are somewhat protected as such from ultraviolet light, and protection should be continued if transferred to another vial.

Oral Preparations

Drug interactions can change the diffusibility, dissolution rate, and particle size of orally administered drugs. Many drugs bind luminal contents (drug-diet interactions; Table 2–3), and oral absorption is impaired (Toothaker and Welling, 1980). On the other hand, the oral absorption of selected drugs is enhanced in the presence of food (see Table 2–3). The effect of food is most important for drugs with a narrow therapeutic window and for drugs with a steep dose-response curve, for which a small change in PDC can cause profound differences in response to the drug. Food can alter splanchnic blood flow, gastric motility (and thus mixing and drug dissolution as well as gastric emptying), and gastric secretions. Changes in gastric secretions can alter gastric pH, which can change the percentage of ionized and thus diffusible drug. The net effect of food on drug absorption depends on the pK$_a$ of the drug, whether the drug is labile to the effects of pH and enzymes, and the site of absorption of the drug (i.e., stomach vs. intestine; (Toothaker and Welling, 1980).

Drug-drug interactions in the gastrointestinal tract can inactivate or prevent absorption of drugs. Sucralfate, cimetidine, aluminum hydroxide, and attapulgite (Kaopectate) are examples of drugs that bind to and prevent the absorption of many drugs. Other drugs alter the rate of absorption by altering gastric motility (Table 2–4; see also discussion

Table 2–2. Examples of Drug Interactions in Solution

Drug or Drug Class	Incompatible Drugs	Other Risks
Amino acid solutions	Many drugs	
Aminoglycosides	Semisynthetic β-lactams, heparin; many others, check manufacturer's label	Adsorbs to glass; use plastic for monitoring
Aminophylline	Do not mix with other drugs	
Amphotericin B	Use only 5% dextrose (or manufacturer suggests sterile water) Do not mix with other drugs	Light exposure
Ampicillin sodium	Selected diluents and drugs; check with manufacturer's label	
Atropine sulfate	Bicarbonate, methicillin, promazine, warfarin, others	
β-lactams		
Cephalosporins	Many drugs, depending on specific antimicrobial; check manufacturer's label	Check manufacturer's recommendations regarding stability upon reconstitution
Penicillins	As for cephalosporins; aminoglycosides	
Bicarbonate	Many drugs	
Buprenorphine	Do not mix with dimenhydrinate, pentobarbital	
Butorphanol	Do not mix with diazepam	
Blood, red blood cells	Any intravenous solution except 0.9% saline	
Calcium-containing solutions	Many drugs	
Calcium disodium EDTA	Do not mix with many drugs, including dextrose, metal salts	
Chloramphenicol	Many drugs	See also Table 2–7
Carbenicillin disodium	Do not mix with many drugs	
Cefazolin	Do not mix with any other drug	
Cephalothin	Do not mix with any other drug	
Diazepam	Cloudiness when mixed with many other drugs indicates precipitation, which will include drug; potency may be reduced	Adsorbs to intravenous tubing and plastic containers Protect from light
Digitoxin (not digoxin)	Calcium, epinephrine, vitamin B complex	
Diphenhydramine	Furosemide, methylprednisolone, pentobarbital	
Dobutamine	Alkaline solutions	Check manufacturer's label regarding discoloration
Doxorubicin	Bicarbonate, heparin, insulin, others	Avoid prolonged contact with aluminum
Doxycycline	Selected drugs, including lidocaine, heparin, isoproterenol, vitamin B complex	
Epinephrine	Calcium-containing solutions, ampicillin, other penicillins, pentobarbital, prochlorperazine, others	
Erythromycin	Several drugs, including selected cephalosporins, chloramphenicol, heparin, tetracyclines, and vitamin B complex	
Flunixin meglumine	Most solutions	
Furosemide	Acidic solutions cause hydrolysis; precipitates when combined with many drugs	Yellow discoloration; protect from light
Gentamicin	Many drugs, including dopamine, furosemide, heparin (see also β-lactams, amphotericin B)	
Glycopyrrolate	Alkaline solutions Avoid diluting with saline or bicarbonate for intravenous infusion Other drugs	Strongly acidic solution
Heparin	Many drugs	Strongly acidic solution Slightly yellow discoloration is okay
Hydrocortisone sodium esters	Acid pH causes hydrolysis. Incompatible with many selected drugs	Use proper dilution volume to avoid precipitation
Imipenem		Do not freeze
Insulin	Check package label regarding diluents and refrigeration need and mixing lente insulin kinetics; incompatible with many drugs	Binds to intravenous tubing, selected types of glass, and plastics
Iron dextran	Oxytetracycline, sulfonamides	
Kanamycin	See gentamicin, aminoglycosides	
Ketamine	Barbiturates, diazepam	
Lidocaine	Alkaline solutions	Loss of drug when stored in polyvinyl chloride bags (adsorption to polyvinyl chloride)
Magnesium sulfate	Many drugs, including calcium-containing drugs, sodium bicarbonate, tetracyclines, others	
Mannitol	Blood, strongly acidic or alkaline solutions	Crystallization of high (25%) concentrations in glass containers generally can be redistributed by warming; crystallization in plastic solutions is difficult to resolve

Table 2–2. Examples of Drug Interactions in Solution *Continued*

Drug or Drug Class	Incompatible Drugs	Other Risks
Methylprednisolone sodium succinate	Normosol-R, Normosol-M, selected drugs	Avoid diluting with a volume that is too small; precipitation may occur otherwise
Metronidazole		Reconstituted lyophilized product very acidic and must be buffered with bicarbonate. Ready-to-use product requires no additional handling. Light sensitive; however, discoloration induced by light not accompanied by loss of potency. Do not freeze
Metoclopramide	β-Lactams, erythromycin, sodium bicarbonate	Protect from light
Morphine	Many drugs	
Multiple vitamin	Bicarbonate, selected cephalosporins, aminophylline, others	Lack of potency loss has been documented; complexes 8 hours after dilution
Nitrofurantoin	Many drugs	
Oxyglobin	Vitamin K (see Phytonadione)	Removal from foil wrap exposes hemoglobin to oxidation with subsequent formation of methemoglobinemia (indicated by brown discoloration)
Oxytetracycline	See tetracycline	
Oxytocin	Do not mix with any other drug	Refrigerate at <25°C; do not freeze
Penicillin G	See also β-lactams Polyethylene glycol Prochlorperazine, pentobarbital, sulfadiazine Others	Rapidly inactivates in pH <6–7 or >8
Pentobarbital	Acid pH Many drugs	Prepared as extremely alkaline solution
Phenobarbital	Many drugs, especially acidic solutions	
Phenylephrine	Penicillin, pentobarbital, phenobarbital, phenytoin, sodium bicarbonate	
Phenytoin	Do not mix with any other drug or intravenous solution	
Phytonadione	Do not mix with ascorbic acid, barbiturates, phenytoin	
Potassium chloride	Do not mix with amphotericin B	
Pralidoxime chloride (2-PAM)	Reconstitute with sterile water only; do not mix with any other drug	
Procaine	Many solutions, especially alkaline	
Procainamide	Dextrose	Light yellow but not amber discoloration okay
Prochlorperazine	Many drugs; do not mix in same syringe	
Promazine	Many drugs	
Promethazine	Selected drugs	
Protein hydrolysate	Many drugs	
Propofol	Do not mix with any other drugs	
Propranolol	Rapidly decomposes in alkaline solution	
Ringer's lactate	Alcohol in 5% dextrose, epinephrine, oxytetracycline, sodium bicarbonate, sulfadiazine	
Sodium bicarbonate	Many drugs; check package insert	
Sodium iodide	Several drugs	
Sulfonamides, sodium salts	Many drugs	
Tetracycline	Highly acidic solution may render incompatible with many drugs	Dark solution indicates decomposition; discoloration in multiple electrolyte solution does not indicate potency loss
Thiopental	Many drugs	
Vancomycin	Selected drugs	
Vitamin B complex	Magnesium sulfate, erythromycin, selected others	
Warfarin	Many drugs	

of pharmacokinetic interactions later in this chapter). To minimize these effects, none of these drugs should be given simultaneously with another orally administered drug.

Topical Preparations

Pharmaceutical interactions in topical preparations may occur between drugs or between drugs and the vehicle in which they are carried (Idson, 1983; Boothe, 1987). Both the rate and extent of drug absorption can be affected adversely. For example, macromolecular additives may bind chemically with the active drug. Methyl, ethyl, hydroxyethyl, and carboxymethyl cellulose frequently form complexes with drugs that can lead to drug precipitation. Vehicles are often selected because of their effect on drug absorption. For example, retardant vehicles (e.g., polyethylene glycol 300) interact with the drug, decreasing its absorption, whereas dimethylsulfoxide (DMSO) is well recognized for its ability to enhance absorption of many topically applied drugs.

The concentration of drug available for skin penetration depends on its dissolution in the vehicle. Few drugs are

Table 2–3. Examples of Drug-Diet Interactions

Decreased absorption	
	Ampicillin
	Erythromycin (film-coated tablets)
	Lincomycin
	Rifampin
	Sulfafurazole
	Tetracyclines
	Theophylline
Delayed absorption	
	Cefaclor
	Cephalexin
	Cimetidine
	Digoxin
	Fluorinated quinolones
	Metronidazole
Enhanced absorption	
	Diazepam
	Erythromycin
	Griseofulvin (fats)
	Imidazoles (decreased pH)
	Metoprolol
	Propranolol

From Toothaker RD, Welling PG: The effect of food on drug bioavailability. Annu Rev Pharmacol Toxicol 1980; 20:173–199.

sufficiently soluble to be dissolved in petrolatum bases; most drugs mixed in such bases are present as particles. Dissolution of drug in the particles is very slow, and few particles are located at the vehicle-skin interface. Drugs must generally dissolve in an aqueous layer of fluids that collects under the ointment base before percutaneous absorption can occur. The solubility of a drug in the vehicle is an important determinant of drug movement into the skin. Water-soluble drugs tend to have a low affinity for the vehicle and are not well absorbed. Lipid-soluble drugs are better absorbed. A drug that has too great an affinity for the vehicle may not, however, be well absorbed simply because it will not leave the vehicle (Boothe, 1987).

Pharmacokinetic Drug Interactions

Drug interactions that occur inside the body may be life-threatening. Pharmacokinetic interactions occur when one drug alters the disposition of another drug (Pond, 1984). Each stage of disposition of a drug—absorption, distribution, metabolism, or elimination—can be altered by another drug.

Absorption

Absorption of one drug may be hindered due to changes in the drug's passage through biologic phases and to changes in local pH, the integrity of biologic membranes, regional blood flow, and, in the case of orally administered drugs, gastrointestinal motility. Each of these changes can be induced by a concurrently administered drug. Examples to consider include the following:

1. Use of an antisecretory drug may decrease the proportion of a weak acid that is orally absorbed as gastric pH is increased, thus decreasing the absorption of weak acids.
2. Similarly, the efficacy of sucralfate, which requires activation by an acidic environment, may be decreased if administered during the peak antacid effect of an antisecretory drug.
3. Sucralfate and cimetidine are examples of drugs that bind to and prevent the absorption of other drugs. Likewise, tetracycline and enrofloxacin are bound by divalent or trivalent cations that might be found in antacids (see Table 2–4).
4. Drugs that alter gastric motility might alter the rate of oral drug absorption. Most drugs are absorbed from the small intestine. Administration of anticholinergics decreases gastric emptying, allowing a longer time to elapse before a drug moves to the small intestine. Although extent of absorption may not be affected, peak plasma drug concentrations may be lower. Metoclopramide probably has an opposite effect. In contrast to gastric motility increasing motility of the small intestine is unlikely to alter the oral absorption of drugs because the surface area is so large it is difficult to manipulate. However, a few drugs alter drug absorption by causing malabsorption or changing gastric blood flow (Table 2–5).

Distribution

Pharmacokinetic drug interactions that alter drug distribution usually result from competition for protein-binding sites between two or more concurrently administered drugs. Because protein binding is reversible, the drug with the highest affinity for protein (usually albumin) displaces the drug with less affinity (Table 2–6). If a highly (>80%) protein-bound drug is displaced by only a small fraction, the amount of unbound, pharmacologically active drug markedly increases, and the risk of toxicity is initially increased. Because nonsteroidal anti-inflammatory drugs (NSAIDs) are generally more than 90% protein bound, even slight displacement of the drug from its binding sites can result in toxic concentrations. Increased hepatic clearance of the unbound drug may ultimately, however, counter increased PDC, and the risk of toxicity may decrease as steady-state concentrations are reached. Most drug interactions involving protein binding also involve

Table 2–4. Examples of Drugs That Affect Gastric Motility

Decreased motility	Increased motility
Anticholinergics	Cholinergics
Adrenergics	Metoclopramide
Neuroleptics	Cisapride
Antihistamines	Antacids
Opioid analgesics	Erythromycin

Table 2–5. Examples of Drugs That Alter Drug Absorption

Drugs that may cause malabsorption	
	Chloramphenicol
	Tetracyclines
	Neomycin
Drugs that may alter regional blood flow	
	α-Adrenergics (decrease)
	Cimetidine (liver)
	β-Blockers

Table 2–6. Highly Protein-Bound Drugs

- Weak acids (albumin)
  - Nonsteroidal anti-inflammatories
  - Coumarin derivatives
  - Antibiotics
    - Doxycycline
    - Minocycline
  - Anticonvulsants
    - Valproic acid
    - Phenytoin
    - Diazepam
  - Furosemide
- Weak bases (α-glycoproteins)
  - Several cardiac drugs
  - Propranolol
  - Lidocaine (some species)
  - Tricyclic antidepressants

competition for albumin-binding sites because albumin is the most common binding protein, particularly for weak acids. Lipoproteins, globulins (increased with acute-phase protein increase), and, to a lesser extent, albumin bind weak bases (e.g., bupivacaine, lidocaine) (see Table 2–6).

Use of drugs that alter drug distribution to peripheral organs can alter drug delivery to the organs. For example, drug therapy for the critical care patient may be ineffective if the patient is hypovolemic. Because blood flow to the brain and heart are maintained, drug that might have been distributed to peripheral organs is distributed to these two organs, increasing their risk of toxicity. In contrast, it should be expected that drug distribution to peripheral organs is likely to increase as the management of a critical care patient progresses and physiologic responses to shock and so forth are medically resolved. Rarely, drug interactions can occur at the tissue site. For example, drugs can compete with each other at tissue-binding sites. Quinidine increases digoxin toxicity because it displaces digoxin from cardiac tissues; in contrast, hypokalemia facilitates binding of digoxin to cardiac tissue, thus enhancing digoxin cardiotoxicity.

Metabolism

Pharmacokinetic drug interactions frequently alter the metabolism of a concurrently administered drug (Table 2–7) (Hostetler et al., 1988; Ohnhaus et al., 1983; Bresnick, 1982; Snyder and Remmer, 1979; Schenkman and Kupfer, 1982). When administering a drug metabolized by the liver, it is wise to anticipate a drug interaction if a second drug also metabolized by the liver is added to therapy. Most of the interactions result from modulation of hepatic (phase I) drug metabolizing enzymes. Many drugs induce enzyme activity (see Table 2–7). The rate of metabolism and clearance of concurrently administered drugs that are metabolized by the liver may thus be increased. Some drugs are capable of both induction and inhibition. The usual sequelae of enzyme induction are increased clearance and decreased pharmacologic response. However, toxicity may be enhanced because of increased production of a toxic metabolite, or, in the case of pro-drugs, increased amounts of pharmacologically active drug are formed. Enzyme induction is probably important in the pathogenesis of hepatotoxicity induced by several drugs (e.g., anticonvulsants) and in the therapeutic failure that accompanies some drugs (e.g., anticonvulsants). Several days to weeks of drug administration generally are required for induction to occur. Induction is usually accompanied by increased hepatic RNA and thus protein synthesis, and an increase in hepatic weight. Phenobarbital is one of the most potent microsomal enzyme inducers known and can enhance the hepatotoxicity of other hepatotoxic drugs. Likewise, it increases the formation of and response to pro-drugs and decreases the effects of itself and other drugs metabolized by the liver as clearance of these drugs is increased (Pond, 1985; Vessey, 1982; Griffin and D'Arcy, 1979).

Table 2–7. Examples of Inducers and Inhibitors of Drug Metabolizing Enzymes

Inducers	Inhibitors
Chlorinated hydrocarbons	Chloramphenicol
Griseofulvin	Cimetidine
Phenobarbital (and other barbiturates)	Fluorinated quinolones
Phenylbutazone	Ketoconazole
Phenytoin	Phenylbutazone
Rifampin	Prednisolone
	Quinidine
	Theophylline

Drug-induced enzyme inhibition (see Table 2–7) may also occur, although it may not be as clinically significant as induction (Netter, 1982). Generally, clearance of a concurrently administered drug metabolized by the liver is prolonged. The potential for toxicity or for an exaggerated pharmacologic response is increased. Pro-drugs (e.g., enalapril, primidone) are less likely to be activated. In contrast to induction, inhibition may occur rapidly. Often inhibition reflects competition for the same metabolic enzymes. Chloramphenicol and cimetidine are examples of potent microsomal enzyme inhibitors (Pond, 1985; Vessey, 1982; Griffin and D'Arcy 1979). Coadministration with potentially toxic drugs that are also metabolized by the liver should be done cautiously. Fluorinated quinolones such as enrofloxacin can increase theophylline plasma concentrations to toxic levels, presumably due to impaired hepatic clearance of theophylline (Pond, 1985; Vessey, 1982; Griffin and D'Arcy, 1979). Ketoconazole impairs the hepatic elimination of several drugs. Alcohol and 4-methylpyrazole competitively inhibit alcohol dehydrogenase, the drug metabolizing enzyme that converts ethylene glycol to its lethal metabolite.

Drug-induced inhibition of drug metabolism can be used for therapeutic benefit. Ketoconazole might be used to decrease the clearance (and thus the dose and cost) of cyclosporine. Enzyme inhibition has been used clinically for cats suffering from acetaminophen toxicity. Because acetaminophen is metabolized by phase I enzymes to a toxic metabolite (which overwhelms glutathione scavenging activity), cimetidine might be used to decrease the production of the potentially fatal toxic metabolite. The combination of cilastatin with imipenem is another example of drug inhibition used therapeutically: Cilastatin inhibits renal tubular drug metabolism of imipenem, thus reducing its hepatotoxicity while prolonging its drug elimination

Table 2–8. Drugs That Compete for Renal Tubular Secretion

- Anions (acidic drugs)
  - Penicillins
  - Cephalosporins
  - Probenecid
  - Sulfonamides
  - Aspirin
  - Furosemide
  - Nonsteroidal anti-inflammatories
  - Phase II metabolites (gluconic acids, glycine, and sulfate conjugates)
- Cations (basic drugs)
  - Procainamide
  - Dopamine
  - Trimethoprim
  - Several opioid agents

half-life. Nutrition, sex, age, and other factors can influence how drug metabolizing enzymes respond to drugs.

Drug clearance may also be affected by drugs that change hepatic blood flow. This interaction is significant, however, only for drugs that are characterized by extensive and rapid hepatic clearance (e.g., propanol, lidocaine) and probably is not clinically relevant at this time.

Excretion

Pharmacokinetic drug interactions may alter urinary excretion due to changes in glomerular filtration, competition between the drug for active tubular secretion, or both. Competition for carrier proteins responsible for active tubular secretion usually involves acidic drugs (Table 2–8). Probenecid is still occasionally used to prolong the elimination of an expensive penicillin because it competes with the penicillin for a carrier protein. Renal excretion may also be affected by drugs that alter urinary pH and tubular reabsorption. Changes in urinary pH conducive to formation of a greater proportion of un-ionized drug (e.g., an acidic urinary pH and an acidic drug) encourages tubular reabsorption of a drug, thus decreasing its clearance and prolonging its elimination half-life (Table 2–9) (Pond, 1985; Vessey, 1982; Griffin and D'Arcy, 1979). For example, overdosing of some drugs (e.g., aminoglycoside or strychnine poisoning) can be treated by hastening elimination with urinary acidifiers.

Pharmacodynamic Drug Interactions

Pharmacodynamic drug interactions occur when one drug directly alters the chemical or physiologic response to another drug (Table 2–10). Pharmacodynamic interactions can enhance the response of a drug due to additive or synergistic effects at the same receptor (e.g., the permissive effect of glucocorticoids on β-adrenergic receptors); at an intracellular site (e.g., epinephrine and theophylline in bronchial smooth muscle), or at different sites but with the same physiologic reaction (e.g., hypokalemia induced by cardiac glycosides and diuretics; many interactions of antibiotics). Pharmacodynamic interactions may decrease the response of some drugs due to competitive antagonism at the same receptor site (e.g., atropine and anticholinesterases or atropine and metoclopramide) or due to antagonistic responses mediated at distant, but physiologically related sites. Antagonistic pharmacodynamic interactions have been used therapeutically: oxymorphone reversal with naloxone; and xylazine and other chemical sedative reversals with tolazoline or yohimbine.

Table 2–9. Examples of Drugs Capable of Changing Urine pH

- Urinary acidifiers
  - Ascorbic acid
  - Methionine
  - Sodium acid phosphate
  - Ammonium chloride
- Urinary alkalinizers
  - Sodium bicarbonate, citrate, and acetate
  - Carbonic anhydrase inhibitors

Table 2–10. Examples of Pharmacodynamic Drug Interactions

Beneficial

- Neuroleptics before anesthesia
- Reversal of narcotics or other sedatives

Detrimental (Increased Toxicity)

Aminoglycosides

- Ototoxicity and nephrotoxicosis increased with furosemide
- Nephrotoxicity increased with NSAIDs
- Neuromuscular effects potentiated by most general anesthetics
  - Especially halothane, barbiturates
  - Reversed with Ca^{2+} and anticholinesterase antagonist
- Enhanced neuromuscular blockade of non-depolarizing agents
  - Lincomycin
  - Clindamycin
  - Polymyxins

Tetracyclines

- May cause neuromuscular blockage when used with general anesthetics (or during hypocalcemia)

Cardiac Glycosides

- Toxicity is enhanced by hypercalcemia, hypomagnesemia, hypokalemia, and hypothyroidism
  - Coadministration of quinidine and furosemide
  - Coadministration of phenobarbital
  - Toxicity can be treated with propranolol or phenytoin

Halothane and Methoxyflurane

- Sensitize myocardium to arrhythmogenic effects of catecholamines
  - Thiobarbiturates potentiate the effect
  - Premedication with acepromazine, lidocaine, or propranolol reduces this effect

Diamidine Antiprotozoals

- Are anticholinesterase inhibitors and potentiate organophosphate intoxication

Succinylcholine

- Is potentiated by cholinesterase inhibitors

Propranolol

- Precipitates hypoglycemia in persons with insulin-dependent diabetes mellitus

Quinidine and Procainamide

- Potential muscle relaxants

Methoxyflurane and Tetracyclines

- May cause fatal renal failure

Amphotericin B and Digitalis Glycosides

- Enhanced cardiac arrhythmias

Phenytoin

- With long-term phenobarbital or primidone causes cholestatic hepatopathy

The most familiar pharmacodynamic interactions are probably those that act in an additive or synergistic manner to augment response to a drug. Augmentation can occur through different mechanisms of action (i.e., controlling vomiting by combining a drug active at the chemoreceptor triggering zone with a drug that acts peripherally; controlling seizures by combining phenobarbital with bromide; controlling tachycardia by combining diltiazem with digoxin). Less commonly, augmentation may occur through similar actions at a receptor site; more often, drugs will compete with one another at the same receptor, thus resulting in antagonism. Unfortunately, we often forget that if the desired pharmacologic response is augmented by drug combinations, often the adverse reactions to the drugs are also augmented. For example, drugs that impair renal prostaglandin synthesis (e.g., NSAIDs, angiotensin-converting enzyme inhibitors, aminoglycosides) should be used in combination cautiously because their combination increases the risk of renal failure. Likewise, ulcerogenic drugs (NSAIDs, glucocorticoids) enhance the risk of gastrointestinal ulceration when used in combination.

Pharmacodynamic interactions may decrease the response to a drug due to competitive antagonism at the same receptor site. Most commonly, these actions are desirable and are frequently the target of combined drug therapy: atropine to treat organophosphate toxicity; reversal agents for opioids and anesthetic agents. Antagonistic pharmacodynamic responses can also occur through different receptor sites or different mechanisms. The combination of a "bacteriostatic" antibiotic with a "bactericidal" antibiotic might be considered as an example. Also, the prokinetic effects of cisapride and metoclopramide are prevented by anticholinergics; the effects of sucralfate are reduced in the presence of high gastric pH induced by antisecretory drug; and calcium-containing solutions should not be combined with blood or blood components because the loss of anticoagulant effects increases the risk of microthrombi formation in the transfused blood.

PATHOLOGIC FACTORS

The diseased patient is more likely to react adversely to a drug. Although such reactions occasionally reflect disease-induced differences in receptor number or sensitivity, most often they reflect differences in drug disposition. The dosage regimens recommended for a pharmaceutical preparation generally are based on controlled studies in the normal, healthy animal. Drugs are most frequently, however, administered to the diseased patient. Pathophysiologic changes in most body systems can alter all phases of drug disposition, predisposing the patient to adverse drug reactions. The sequelae of disease on drug disposition usually lead to increased PDCs and thus to a greater potential for adverse drug reactions. Occasionally, however, PDCs are lower than anticipated, and therapeutic failure may occur. Diseases most likely to contribute to adverse drug reactions are those affecting the kidneys, liver, and heart. Less significant effects accompany gastrointestinal, pulmonary, endocrine, and metabolic disorders.

Renal Disease

Drug toxicity in renal failure may result either from increased sensitivity to the drug due to uremia-induced alterations in tissue receptors or from decreased or increased PDCs caused by disease-induced changes in pharmacokinetics. The latter have been best characterized (Brater and Chennavasin, 1985; Stern, 1983; Riviere, 1984; Carlson and Kaneko, 1971) (Table 2–11).

Renal blood flow is often profoundly decreased in patients with renal disease. Changes in glomerular filtration and tubular secretion tend to parallel changes in renal blood flow. The effects of changes in renal blood flow (usually decreased) on drug excretion are most profound if renal extraction of the drug is high (e.g., penicillins, sulfates, and glucuronide conjugates) but are less significant for drugs that are slowly extracted (e.g., aminoglycosides, diuretics, digoxin).

Glomerular filtration of drugs and other compounds is also adversely affected in renal disease independent of changes in renal blood flow. The determinants of glomerular filtration include protein binding, glomerular integrity, and the number of functional (filtering) nephrons. The molecular size of the drug is also important because drugs with a molecular weight greater than approximately 70,000 usually cannot be filtered. Drugs that are tightly protein bound (such as NSAIDs) are not filtered until they are displaced from the protein. Factors that tend to displace such drugs from protein-binding sites may increase the rate of drug excretion in renal disease and include hypoalbuminemia, competition for protein-binding sites due to accumulation of uremic toxins, or changes in the conformation and thus binding affinity of the protein (e.g., albumin). Changes in protein binding that have been measured in renal disease include decreased binding of acidic drugs (e.g., furosemide, NSAIDs, and selected penicillins and anticonvulsants) and normal or increased binding of basic drugs due to increased concentrations of inflammatory proteins (e.g., propranolol, diazepam, prazosin).

Although changes in active tubular reabsorption that may accompany renal disease probably do not profoundly influence the rate of drug excretion, changes in active tubular secretion can be significant. Active tubular secre-

Table 2–11. Examples of Drugs Characterized by Changes in Drug Disposition in Patients with Renal Disease

- Changes in protein binding (decreased)
  - Furosemide
  - Naproxen
  - Phenylbutazone
  - Salicylate
  - Warfarin
- Changes in volume of distribution (increased)
  - Cefazolin
  - Furosemide
  - Naproxen
- Changes in clearance
  - Aminoglycosides
  - β-lactams
  - Digoxin
  - Sulfates
  - Furosemide

tion occurs in the pars recta (straight segment) of the proximal tubule. A transport system exists for a variety of organic acids (e.g., penicillins, cephalosporins, NSAIDs, sulfonamides, and several diuretics) as well as bases (e.g., cimetidine, procainamide, and some morphine derivatives). Distal nephron active transport may also be important for some drugs (e.g., digoxin). Excretion of these drugs is most likely to be decreased in the presence of renal disease due to decreased nephron mass, decreased renal blood flow, and decreased tubular function.

In addition to these changes, renal disease can also alter drug disposition because of changes in electrolyte, acid-base, and fluid balance. Changes in electrolytes and acid-base balance may also be important in altering receptor sensitivity to drugs, such as those affecting the cardiovascular system (e.g., hyperkalemia and its effects on responses to digitalis, quinidine, and procainamide).

For drugs whose elimination depends on renal function and whose clearance is known to be decreased in renal disease (see Table 2–11), dosing regimens can be appropriately altered to reduce the incidence of adverse reactions (Riviere, 1984). Either serum creatinine or creatinine clearance is generally used to estimate glomerular filtration rate; however, because of its ease of measurement, serum creatinine is most commonly used. Decreases in the renal elimination of a renally excreted drug tend to parallel increases in serum creatinine, and dosing regimens can be altered by either lengthening the dosing interval or decreasing the dose by a proportional decrease in creatinine clearance or the increase in serum creatine:

$$\text{New dose} = \text{old dose} \times \frac{\text{pt CrCl}}{\text{normal CrCl}} \text{ or } \times \frac{\text{normal Cr}}{\text{pt Cr}}$$

$$\text{New interval} = \text{old interval} \times \frac{\text{normal CrCl}}{\text{pt CrCl}} \text{ or } \times \frac{\text{pt Cr}}{\text{normal Cr}}$$

where pt is patient, Cr is creatinine, and Crcl is creatinine clearance. For example, if a patient has a serum creatine level of 2.5 mg/dL (normal is 1.2), a dosing interval for a drug given every 12 hours would be prolonged to every 24 hours, or the dose of 2 mg/kg could be reduced to 1 mg/kg.

The parameter of the dosing regimen that should be altered depends on the drug. Lengthening the interval results in wider swings in PDCs during a single dosing interval and thus may not be desirable for antimicrobial therapy or anticonvulsant or cardioactive drugs that depend on maintenance of a minimum drug concentration within a specified therapeutic range. Thus, decreasing the dose may be more appropriate for these drugs. For drugs with a long elimination half-life or for drugs whose effects persist in the absence of detectable drug (e.g., selected antibiotics, glucocorticoids, nonsteroidal agents), however, it may be more appropriate to prolong the interval. For example, gentamicin's efficacy depends on a high PDC. Safety is based on allowing PDCs to fall below a recommended trough concentration. Thus, prolonging the interval is more appropriate than lowering the dose for gentamicin. As such, for a patient with a serum creatine level of 2.5 mg/dL (normal is 1.2), a dosing interval for gentamicin of every 12 hours would be prolonged to every 24 hours, but the old dose would be given. For other drugs (e.g., a potentially toxic β-lactam antibiotic), the dose might be decreased by 50%, but the old interval is used.

Hepatic Disease

The efficiency of hepatic elimination is determined by hepatic clearance and by the hepatic extraction ratio of the drug (Wilkinson and Shand, 1975; Wilkinson and Branch, 1984; Ahmad et al., 1983; Boothe, 1995). Both, in turn, depend on hepatic blood flow, the extent of drug protein binding, and intrinsic hepatic clearance, which itself consists of hepatic uptake (the rate-limiting step of hepatic clearance), intracellular transport, metabolism, and, if applicable, biliary elimination. Drugs that are eliminated by the liver can be categorized based on their rate of extraction (Williams, 1984). *Flow-limited* drugs (e.g., lidocaine, propranolol, and verapamil) are so rapidly extracted by the liver that their rate of elimination depends only on the rate at which it is delivered to the liver (e.g., hepatic blood flow). Such drugs are insensitive to changes in hepatic metabolism but are very sensitive to changes in hepatic blood flow. *Capacity-limited* drugs (e.g., diazepam, prednisolone, phenylbutazone, phenytoin, theophylline, cimetidine, and antipyrine) are extracted slowly by the liver, and their elimination depends on hepatic uptake and metabolism but is independent of hepatic blood flow. The elimination of such drugs is affected by changes in hepatic metabolism but not by changes in hepatic blood flow. Some drugs are intermediate, being partially dependent on hepatic blood flow and hepatic metabolism (Williams, 1984; Wilkinson and Branch, 1984).

Protein binding can affect the elimination of some of these drugs because only unbound drug can be extracted by the liver. Flow-limited drugs tend to be *binding insensitive* in that hepatic extraction is so fast that binding to proteins does not alter their rate of elimination. Some capacity-limited drugs are not significantly protein bound and thus are also binding insensitive (e.g., antipyrine). In contrast, some capacity-limited drugs are *binding sensitive* (e.g., theophylline, phenytoin) because their slow rate of extraction can be increased by decreasing or increasing, respectively, protein binding (Blashke and Rubin, 1989a).

The effects of hepatic disease on drug disposition are very complex, particularly for drugs that are affected by changes in hepatic blood flow, hepatic metabolism, and protein binding (Table 2–12) (Williams, 1984; Wilkinson and Branch, 1984). Each of these parameters may be altered in various ways in patients with liver disease. Hepatic blood flow is generally reduced in chronic liver disease. The presence of portal-systemic shunts contributes to reduced blood flow. In addition, intrahepatic shunting of blood flowing through the liver reduces drug delivery past functional hepatocytes. Thus, the clearance of highly extracted drugs is generally reduced in patients with liver disease. Plasma and tissue drug concentrations are markedly higher when dosing regimens are not appropriately altered. This is particularly important for highly extracted

Table 2–12. Drugs Characterized by Changes in Drug Disposition in Patients with Hepatic Disease

- Changes in blood flow: Flow-limited drugs
  - Lidocaine
  - Meperidine
  - Metoprolol
  - Morphine
  - Pentazocine
  - Propranolol
  - Verapamil
- Changes in metabolism: Capacity-limited drugs
  - Chloramphenicol
  - Cimetidine
  - Diazepam
  - Furosemide
  - Prednisolone
  - Ranitidine
  - Theophylline
  - Warfarin
- Changes in protein binding
  - Lidocaine
  - Meperidine
  - Propranolol
  - Diazepam
  - Phenylbutazone
  - Phenytoin

From Williams RL: Drugs and the liver: Clinical applications. In Benet LZ, Massoud N, Gambertoglio JG (eds): Pharmacokinetic Basis for Drug Treatment, pp 53–75. New York, Raven Press, 1984.

drugs when they are administered orally. The dose of such drugs (e.g., propranolol, verapamil, prazosin, morphine derivatives) in the presence of normal hepatic blood flow is based on decreased bioavailability due to "first-pass" extraction: A large percentage of the drug does not reach systemic circulation because it is removed from portal blood by the liver the first time it passes through the liver. Decreased hepatic blood flow and intrahepatic shunting of blood can markedly increase systemic bioavailability of such drugs (Blashke, 1989). Recent studies in human patients with liver disease suggest that the intrinsic metabolism of highly extracted drugs is also reduced in patients with liver disease. In human patients with liver disease, the dose of many highly extracted drugs is reduced by 50%; such an approach is probably reasonable for the veterinary patient.

The effect of liver disease on poorly extracted (capacity-limited) drugs is more difficult to predict, particularly for drugs highly protein bound. Generally, hepatic metabolism is reduced in patients with liver disease. Disease is generally quite profound, however, by the time changes in drug disposition become evident. The severity of disease is manifested as a decrease in serum albumin and blood urea nitrogen levels (but not necessarily increased bilirubin). This has been shown by studies that have measured the clearance of antipyrine and caffeine, which are capacity-limited, binding-sensitive and -insensitive drugs, respectively, in dogs with experimentally induced liver disease (Boothe et al., 1992, 1994). Because elimination of these drugs depends entirely on hepatic metabolism, their clearance might be used as a hepatic function test. Because their elimination does not necessarily correlate with the elimination of other drugs that also depend on hepatic clearance, however, they are not yet used to predict changes in dosing regimens for the patient with liver disease. Recommendations regarding dosing regimens for drugs not highly extracted by the liver thus are difficult to make for the patient with liver disease, in part because there is no simple test that will assess or quantitate hepatic function (Morgan and Smallwood, 1989; Poulsen and Loft, 1988; Boothe, 1995; Boothe et al., 1922, 1994; Van Thiel and Hassenein, 1995). In general, clearance of capacity-limited drugs is probably not impaired in patients whose serum albumin and blood urea nitrogen levels are within normal limits. Common sense dictates, however, that discretion be used when administering potentially toxic drugs that depend on hepatic clearance for elimination.

Diseases of the biliary tract alter the disposition of drugs eliminated through the bile. This route of elimination is complex, however, with drugs being eliminated in feces and undergoing enterohepatic circulation. Characterizing these changes is difficult without catheterization of the biliary duct, and recommendations are very difficult to offer. Cholestasis decreases the content or activity of cytochrome P450 drug metabolizing enzymes and thus can affect the elimination of drugs that are not secreted in bile (Rollins, 1984; Kawata et al., 1987). In general, doses of drugs eliminated principally in the bile should be reduced, particularly if the drug is characterized by a narrow therapeutic window. Examples include selected antibiotics (doxycycline and clindamycin), digitoxin, and naproxen.

The effects that changes in protein binding may have on hepatic drug clearance contribute to the unpredictable nature of liver disease-induced changes in drug disposition (Blashke and Rubin 1989; Evans et al., 1973; Belpaire et al., 1987). Decreased protein binding of drugs that may accompany liver disease (i.e., due to decreased synthesis of albumin, competition for binding sites by endogenous compounds, or changes in conformation of the binding site) may increase hepatic clearance and thus compensate for reduced hepatic metabolism. Increased binding may, however, also occur particularly for basic drugs (e.g., lidocaine) due to increased production of acute-phase proteins, which may have the effect of decreasing clearance. Changes in protein binding will also affect drug distribution. Protein binding decreases the amount of drug that distributes to peripheral tissues. Drug distribution in the patient with liver disease will be further complicated by the effects of fluid, electrolyte, and acid-base imbalances, which are also likely to occur. For example, an ascitic compartment may lead to overdosing if a patient is not dosed based on lean body weight and the drug does not distribute to the ascitic compartment, which may constitute up to 30% of body weight (Fig. 2–1).

Cardiac Disease

Cardiac disease profoundly affects drug disposition (Table 2–13). Primary or compensatory disturbances that lead to altered drug disposition include renal sodium and water retention, increased pulmonary and systemic venous pressures, and increased sympathetic nervous system output (Benowitz, 1984). Sodium and water retention can cause profound changes in drug distribution due to changes in the sizes of body compartments. In addition, increased

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Figure 2–1. The ascitic compartment in an animal with liver or other disease can represent up to 30% of body weight. If this compartment is not one to which a drug distributes and the animal is dosed based on total body weight, plasma drug concentrations may be more than 30% higher than expected. If the drug is distributed to the ascitic compartment, the compartment may result in a longer elimination half-life.

sympathetic outflow results in redistribution of blood flow such that the heart and brain receive a higher proportion of blood and thus are exposed to more drug. Because other tissues, particularly skeletal muscle, represent a large volume to which drug is normally distributed, reduced distribution of drug to these tissues results in even higher PDCs in blood going to the heart and brain. Thus, the heart and brain are more susceptible to toxicity. Central nervous system and cardiac toxicities to lidocaine and cardiac toxicity to digoxin have been described in some patients with cardiac disease; these toxicities have been attributed to blood redistribution, which accompanies cardiac failure.

As cardiac output decreases, reduced blood flow to the kidney and liver will have profound effects on clearance of drugs through either of these organs. Reduced blood flow reflects in part redistribution mediated by sympathetic output. As cardiac disease progresses, however, decreases in blood flow to both the liver and kidneys parallel decreases in cardiac output. The effects of decreased hepatic blood flow on drug elimination depend on the drug; as with liver disease, hepatic clearance of flow-limited drugs may be profoundly decreased. In the kidney, sympathetically mediated intrarenal redistribution of blood from cortical to juxtaglomerular tubules increases the likelihood of tubular reabsorption, which prolongs drug half-life.

Table 2–13. Drugs Characterized by Changes in Drug Disposition in Patients with Cardiac Disease

Decreased volume of distribution	Decreased clearance
Lidocaine	Lidocaine
Procainamide	Prazosin
Quinidine	Procainamide
Theophylline	Quinidine
	Theophylline
	Digoxin*

*Clearance of digoxin affected by other drugs used to treat cardiac disease.

From Benowitz NL: Effects of cardiac disease on pharmacokinetics: pathophysiologic considerations. In Benet LZ, Massoud N, Gambertoglio JG (eds): Pharmacokinetic Basis for Drug Treatment, pp 89–104. New York, Raven Press, 1984.

Tissue hypoxia and decreased delivery of nutrients to the kidney and liver also contribute to decreased clearance by these organs. The metabolic capacity of the liver is reduced; thus, clearance of capacity-limited drugs is impaired. Similarly, renal tubular function is impaired.

Drug absorption may be impaired in the patient with cardiac disease. This is particularly true for parenterally administered drugs. The rate of absorption is more likely to be impacted than the extent of absorption; hence peak concentrations may be less, although the extent of drug absorption may not be affected. Redistribution of blood away from skeletal muscle and skin decreases the rate of drug absorption after intramuscular and subcutaneous injections. Autonomic disturbances, consisting of increased sympathetic activity and decreased autonomic tone, tissue hypoxia, and mucosal edema may decrease both the rate and the extent of gastrointestinal absorption. Decreased blood flow to the intestinal villus may potentially decrease absorption of drugs that are normally very rapidly absorbed from the gastrointestinal tract. Finally, the effects of cardiac disease on hepatic clearance of flow-limited drugs and thus on systemic bioavailability of orally administered drugs must be considered.

Several recommendations can be made for administering drugs to the patient with cardiac disease.

1. Critical drugs should be administered intravenously because absorption from all other routes is limited.
2. Drugs that are toxic (particularly to the brain and heart) should not be rapidly administered intravenously (i.e., administer over 10 to 30 minutes).
3. High drug concentrations resulting from redistribution should be compensated for by decreasing loading doses.
4. Maintenance doses of selected drugs cleared by the liver, kidney, or both should probably be lowered, although predicting which drugs and how much is difficult. Therapeutic monitoring should be used to guide alteration of dosing regimens whenever possible.

Thyroid and Other Diseases

Both hyperthyroidism and hypothyroidism can profoundly affect drug disposition, although the manner is unpredictable (Eichelbaum, 1976). The effects thus far involve metabolism. In human patients with hyperthyroidism, the activities of some cytochrome P450 enzymes (e.g., hydroxylation) are increased, while those of others (e.g., N-demethylation) are decreased. In rats in which hyperthyroid disease had been induced, enzymes that act as cofactors were increased. Thyroidectomized animals have a general decrease in drug metabolism, although the sequelae are not always predictable. The effects of thyroid disease on drug disposition also depend on sex, with male rats having a general decrease in cytochrome P450 enzymes. The clinical sequelae of changes in drug disposition induced by thyroid disease are not well described in scientific studies, although several examples are provided in the human literature. Digoxin doses necessary to induce a clinical response are in general increased for patients with hyperthyroidism, whereas smaller doses than normal are needed for patients with hypothyroidism. Interestingly, propranolol clearance is decreased in cats with hyperthyroidism (Whittem, 1996).

Diseases of other body systems can also dramatically alter drug disposition. For example, gastrointestinal disease (such as chronic inflammatory bowel disease) alters absorption of orally administered drugs (Nimmo, 1976). Diseases of any system may alter the response of that system to a drug. Nutrition also can alter drug metabolizing enzymes. The effects of disease, regardless of the system, on drug absorption, distribution, metabolism, and excretion are very complex, often subtle, and very difficult to predict. Finally, as therapy becomes successful and the clinical signs of disease resolve, the sequelae of disease on drug disposition also resolve. Therapy once again may need to be adjusted as the animal responds.

PHYSIOLOGIC FACTORS

Age-Induced Differences

Drug Disposition in the Geriatric Animal

This discussion focuses on some of the clinically important changes that are likely to alter response to drug therapy in geriatric patients and on actions that can be implemented to compensate or reduce the sequelae of these changes. Two major areas of concern are changes in pharmacokinetics (gerontokinetics) or drug disposition and changes in pharmacodynamics or tissue response to drugs (Massoud, 1984; Ritschel, 1988; Feely and Coakley, 1990). The latter concern will focus on both the potential for reduced response to analgesic drug therapy (i.e., therapeutic failure) and the increased likelihood of drug-induced toxicity.

The age at which body functions convert from a period of growth to a period of decay (16 to 18 years in humans) has not been established in dogs and cats. Although humans are not considered to have reached "old age" until 80 years of age, no age has been generally recognized to reflect "geriatric" in dogs and cats. The age probably differs among canine breeds. Aging is accompanied by permanent loss of up to 30% of body cells, with a parallel loss in oxygen consumption. Body composition changes as do regional blood flow rates. Physiologic functions generally decline steadily with increasing age. In humans, basal metabolic rate decreases by 0.4% per year (Ritschel, 1988). Changes in individual body systems that might be important to drug therapy include the following.

Cardiovascular As animals age, cardiac output decreases with an increase in circulation transit time. In humans, cardiac output decreases by about 1% per year for a total decline of 30% to 40% in the aged. Regional and organ blood flow rates similarly decrease (Ritschel, 1988). These changes are likely to induce changes in the disposition (i.e., absorption, distribution, metabolism, and excretion) of drugs (see earlier discussion) (Benowitz, 1984; Aucoin, 1989). These changes can lead to either decreased (i.e., altered absorption and distribution) or increased (i.e., altered distribution, metabolism, or excretion) plasma and thus tissue drug concentration (Ritschel, 1988; Aucoin, 1989). As cardiac function decreases, secondary compensatory responses can lead to further risks of adverse reaction (Aucoin, 1989). Blood flow is preferably redistributed to the brain and heart, increasing the risk of toxicity of drugs toxic to these tissues.

Central and Peripheral Nervous Systems As the geriatric patient ages, brain weight and peripheral fiber numbers decrease. Connective tissue infiltrates peripherally (Ritschel, 1988). Oxygen consumption and cerebral blood flow decrease. In addition, decreased amounts of selected neurotransmitters have been documented.

Respiratory In human geriatric patients, residual lung volume decreases by 50% with accompanying decreases in vital capacity, arterial Po_2, and maximum oxygen uptake. In addition, the central response to hypoxia and hypercapnia, such as that induced by opioid analgesics, decreases (Ritschel, 1988). Anesthetic or other sedating agents must be used more cautiously.

Gastrointestinal As animals age, deglutition decreases due to decreased salivation and to pharyngeal and esophageal motility. Gastric function is characterized by atrophy of the mucosa with a reduction of hydrochloric acid secretion and a subsequent increase in gastric pH. Gastrointestinal motility is generally reduced. The intestinal macrovilli and microvilli also atrophy, increasing the risk of bacterial overgrowth. These sequelae tend to reduce the absorption and thus the PDC of orally administered drugs. Changes in gastrointestinal function may also predispose the geriatric patient to adverse affects induced by toxic drugs such as chemotherapeutic agents and NSAID analgesics. NSAIDs should be used cautiously; the clinician should anticipate and be prepared to treat toxicities (e.g., NSAID gastroulceration with antisecretory drugs (e.g., omeprazole), misoprostol (a prostaglandin E_2 analogue), and sucralfate.

Hepatic Changes in hepatic function are important to the geriatric animal because of the liver's role in the metabolism of drugs (Sheaker and Bay, 1994). Hepatocyte number and function decrease as do hepatic and splanchnic blood flow, hepatic oxidation, and cytochrome P450 content (the primary drug metabolizing enzyme). Both flow-limited and capacity-limited drugs are affected. For example, hepatic clearance of both opioid analgesics (which are characterized by first-pass metabolism; i.e., flow limited) and nonsteroidal analgesics (eliminated principally by hepatic metabolism; i.e., capacity limited) is decreased in geriatric patients. Increased response of human geriatric patients to opioid analgesics—they require 60% to 75% less drug than a younger patient—has been attributed to changes in drug elimination (Enck, 1991; Ritschel, 1988; Workaman et al., 1989). Changes in hepatic function, oxygenation, and nutrition may also predispose the liver to drug-induced hepatotoxicity. Because of reduced hepatic function, the geriatric patient may be less able to generate endogenous hepatoprotectant agents.

Urinary As renal blood flow decreases, the glomerular filtration rate and active secretory capacity of the nephron unit progressively decrease with age. Both result in a similar decline in renal clearance. Renal excretion is the major route of elimination of many drugs. Changes in renal clearance tend to prolong the elimination and thus increase PDCs in the geriatric patient. Changes in renal function also render the geriatric patient more susceptible to adverse drug reactions such as those induced by aminoglycosides, angiotensin-converting enzyme inhibitors, and NSAID analgesics.

Body Weight and Composition Lean body mass decreases as fatty tissues increase (Fig. 2–2). In human males, fat increases from about 18% in young adults up to 50% in the aged (Ritschel, 1988). Increased proportion of body fat is accompanied by a decrease in total body water and cell mass. Although extracellular fluid does not change in total amount, the relative proportion of total body water that it comprises increases. Thus, the proportion of intracellular to extracellular fluid decreases. The sequelae of these changes depend on the drug. As distribution of water-soluble drugs decreases with total body water, PDCs tend to increase. The distribution of lipid-soluble drugs increases as the proportion of body fat increases, however, tending to decrease PDCs unless the patient is dosed on total body weight.

Serum Albumin Although total serum plasma protein content probably remains the same in the geriatric animal, the proportion represented by albumin decreases and that by gamma globulins increases. Changes in serum albumin can be clinically important to patients receiving highly protein-bound drugs, such as NSAIDs. Decreased albumin can result in a greater proportion of free drug: Most NSAIDs are close to 99% protein bound. A decrease of only 1% (i.e., 99% to 98% binding) doubles the concentration of a pharmacologically active drug. The sequelae of increased PDC may be offset by a compensatory increased clearance, because only unbound drugs are generally conducive to hepatic or renal clearance.

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Figure 2–2. Increased body fat in the geriatric (or young) animal is a compartment to which water-soluble drugs generally do not distribute. Failure to dose the animal based on lean body weight (rather than total body weight) with such drugs may result in higher than expected plasma drug concentrations. Distribution of a lipid-soluble drug to the fat compartment, on the other hand, may increase the volume of distribution, decreasing drug concentrations (dosing based on total body weight may help minimize this), and may prolong the elimination half-life.

Receptor Sensitivity Geriatric patients respond differently to some drugs, suggesting that tissue receptor sensitivity to the drugs is altered. Changes in receptor number or responsiveness have been implicated but not documented (Ritschel, 1988; Feely and Coakley, 1990). Physiologic changes such as altered neurotransmission or intracellular constituents have also been suggested. For example, geriatric patients are less likely to perceive, appreciate, or express pain. Thus, the need for analgesic therapy is often not detected. In addition, geriatric patients are less able to respond to many analgesic drugs.

Disease Aged animals are more likely to be suffering from diseases that affect not only drug disposition but also tissue receptivity to drugs (Workaman et al., 1989). The immune system of the geriatric patient is not as effective as that of the adult (Schultz, 1984), leading to the use of bactericidal antibiotics and minimizing the use of immunosuppressive drugs. In addition, the geriatric patient is more likely to be receiving multiple drugs, which increases the likelihood of drug interactions. Finally, diseases of selected organs may predispose these organs to drug-induced toxicity.

Analgesics offer a good example of drugs that must be used cautiously by geriatric patients. The doses of both opioids and NSAIDs should be decreased in anticipation of adverse effects. In human patients, opioid doses are reduced as much as 75% in geriatric patients. For NSAID therapy, antisecretory drugs, misoprostol, or sucralfate should be considered as "protective" for geriatric patients.

Drug Disposition in the Pediatric Animal

With regard to dogs and cats, *pediatric* generally refers to the first 12 weeks of life (Robinson, 1983). Important developmental changes occurring within this time spectrum, however, justify further staging into neonatal (0 to 2 weeks), infant (2 to 6 weeks), and pediatric (6 to 12 weeks) periods of growth. Changes associated with each of these periods cause accompanying changes in drug disposition, thus rendering the pediatric patient more susceptible to drug-induced adverse reactions. All four determinants of drug disposition (i.e., absorption, distribution, metabolism, and excretion) undergo dramatic changes as the neonate matures (Table 2–14) (Green and Mirkin, 1984; Boothe and Tannert, 1991). However, the clinical significance of these sequelae vary.

Absorption After oral administration, most drug absorption occurs from the small intestine. Because the surface area of the small intestine is large, even in neonates, the extent of drug absorption probably does not clinically differ between normal pediatric and adult animals. The rate of absorption tends to be slower, however, probably due to decreased gastric emptying and irregular intestinal peristal-

Table 2-14. Examples of Differences in Drug Disposition in Puppies and Kittens Compared with Adults

Difference	Sequelae	Possible Clinical Significance
Decreased gastric emptying and irregular peristalsis	Slower absorption and lower PDC	Therapeutic failure; dose increase may be indicated
Increased intestinal permeability	Increased rate of oral absorption and higher peak PDC	Toxic concentrations
Increased gastric pH	Increased oral absorption of acid-labile drugs; greater peak and duration of PDC	Toxic concentrations Therapeutic failure
Increased absorption of volatile gases	Decreased absorption of weakly acidic drugs, decreased dissolution of drugs, increased PDC	Increased toxicity
Increased absorption of topically applied drugs	Greater peak and duration of PDC	Toxicity to topically applied drugs or drugs or toxins in the environment
Greater total body water with a greater proportion located extracellularly	Increased distribution of drugs; lower peak PDC, but longer drug half-life	Therapeutic failure; dose increase may be indicated; longer dosing interval may be indicated
Lower concentrations of serum proteins	Decreased binding of significantly protein-bound drugs; increased activity of drug; more drug distributed to peripheral tissues; longer drug half-life?	Toxicity; increased drug accumulation may necessitate longer dosing intervals
Decreased body fat	Decreased accumulation of lipid-soluble drugs; higher peak PDC	Toxicity to drugs distributed to fat

Abbreviations: PDC = plasma drug concentration.

From Boothe DM, Brown SA, Jenkins WL, et al: Disposition of indocyanine green in dogs with experimentally induced dimethylnitrosamine hepatotoxicity. Am J Vet Res 1992; 53:382–388.

sis. As a result, peak PDCs may be lower in pediatric patients. The decreased rate of absorption might actually protect against toxic drug concentrations (Heimann, 1980; Rane and Wilson, 1983). These protective mechanisms may not, however, be present in the neonate before absorption of colostrum. During this period, the permeability of the intestinal mucosa is increased along with the rate and extent of drug absorption. Occasionally, drugs that normally are not absorbed from the gastrointestinal tract (e.g., aminoglycosides, carbenicillin and other acid-sensitive β-lactams, and enteric sulfonamides) can reach systemic circulation. Intestinal permeability decreases rapidly after the ingestion of colostrum (Gillette and Filkins, 1966; Rane and Wilson, 1983), possibly due to endogenous release of hydrocortisone or adrenocorticotropic hormone. Exogenous supplementation of either of these hormones by the 24-hour prepartum mother prevents increased permeability and colostrum absorption in the neonate.

A number of other factors may alter small intestinal drug absorption in pediatric patients. Gastric pH is neutral in the newborn; adult levels are not reached until some time after birth, depending on the species (Heimann, 1980; Gillette and Filkins, 1966). Increased gastric pH (achlorhydria) may decrease the absorption of many drugs that require disintegration and dissolution or are ionized in a less acidic environment (e.g., weak acids such as penicillins). Milk diets can reduce drug absorption by either decreasing gastric emptying or directly interacting with drugs (e.g., milk can impair absorption of tetracyclines). The "unstirred water layer" adjacent to the surface area of the mucosal cells is thicker in the neonate than in the older pediatric patient and may limit the rate of absorption of some drugs. As biliary function matures, the absorption of fat-soluble drugs (e.g., griseofulvin and fat-soluble vitamins) increases. Microbial colonization of the gastrointestinal tract may alter response to antimicrobial drugs, extrahepatic metabolism, or enterohepatic circulation (Morselli et al., 1983; Jones, 1987).

Absorption from the rectal mucosa is rapid. Rectal administration of drugs or fluids can be used for pediatric patients when venous catheterization is difficult, to reduce complications associated with intravenous administration (e.g., sedation or anesthesia), or when oral administration is undesirable (e.g., antiemetics). Several pediatric drugs intended for systemic effects are available as rectal suppositories. Limited data from human infants indicate that peak plasma concentrations after rectal administration may be higher than those obtained by other routes (Morselli et al., 1983).

Absorption of drugs administered parenterally to pediatric animals also varies from adults. The rate of absorption after intramuscular administration changes with age as muscle mass and its accompanying blood flow increase and as vasomotor responses mature (Morselli et al., 1983). Because muscle mass is small, subcutaneous administration is frequently preferred for pediatric patients. Again, variability in subcutaneous absorption rates can be anticipated with age. Less fat but greater water may result in faster absorption compared with that in adults (Shifrine et al., 1973). Environmental temperature probably influences subcutaneous absorption, particularly in newborns whose thermoregulatory mechanism is poorly functional. Cold environments are likely to reduce subcutaneous drug absorption if the neonate is not provided warmth. The same is true for the patient who is in a state of hypothermia. Intraperitoneal administration can be a life-saving route of blood and fluid administration, particularly for the newborn with inaccessible central veins. Isotonic fluids are rapidly absorbed, and up to 70% of red blood cells are absorbed within 48 to 72 hours (Authement et al., 1987). Blood and fluids can also be administered into the medullary cavity of large bones (Fiser, 1990; Hodge, 1987).

Absorption of volatile anesthetics from the pediatric respiratory tract is rapid because minute ventilation is greater (Robinson, 1983). Thus, young animals are more sensitive to the effects of gas anesthetics. Although not a common route of drug administration, percutaneous absorption of drugs is likely to be greater in pediatric patients. Percutaneous absorption is directly related to skin hydration, which is greatest in neonates. Topical administration of potentially toxic lipid-soluble drugs (e.g., hexachlorophene and organophosphates) should be avoided.

Distribution The most important factors contributing to differences in drug distribution in pediatric patients are differences in body fluid compartments and drug binding to serum proteins. Body fluid compartments undergo profound changes with the growth of the neonate. Both the percentage of total body water and the ratio of compartmental volumes change with maturation. The percentage of total body water decreases with age, but the decrease is more substantial in the extracellular versus the intracellular compartment (see Table 2–11) (Sheng and Huggins, 1972). Daily fluid requirements are greater in neonatal and pediatric patients, in part because a larger proportion of their body weight is represented by body water (Fig. 2–3). The sequelae of these body compartment differences depend on the normal distribution of the drug. Most water-soluble drugs are distributed to extracellular fluids. In pediatric patients, the volume to which these drugs is distributed is therefore higher than in adults; PDCs correspondingly decrease. Thus, doses may need to be increased to avoid therapeutic failure. A different pattern might be expected for lipid-soluble drugs because they tend to be distributed to total body water. Such drugs should be dosed on body weight (e.g., mg/kg). Although decreased PDCs resulting from increased distribution may protect the pediatric patient from potentially toxic drug concentrations (Davis et al., 1973), a poor therapeutic response may result from failure to generate therapeutic drug concentrations of water-soluble drugs. Changes in the half-life of each drug parallel changes in distribution. Because many drugs are distributed to a larger volume in pediatric patients, a longer half-life should be anticipated and the dosing interval may need to be prolonged.

Because the proportion of body fat is smaller in pediatric patients, the distribution of lipid-soluble drugs that accumulate in fat (such as organophosphates, chlorinated hydrocarbons, and ultrashort thiobarbiturates) may be proportionately decreased. Although drug half-life would decrease, PDCs may become toxic. Many lipid-soluble drugs have a high affinity for and are bound by plasma proteins, thus facilitating their movement through the body. Binding, however, limits their distribution to tissues. Predicting the distribution of highly protein-bound drugs is complicated in the pediatric patient. Serum concentrations of both serum albumin, the protein to which most drugs are bound, and α_1-glycoproteins (to which basic drugs preferentially bind) are decreased in pediatric patients (Poffenbarger et al., 1990). Protein binding of drugs may also be reduced because of differences in albumin structure or because drugs compete with endogenous substrates (such as bilirubin) for binding sites (Rane and Wilson, 1983; Ehrnebo et al., 1973). As drugs are displaced, the concentration of free, pharmacologically active drugs and the risk of adverse reactions increase. These changes are significant, however, only if the drug is highly (i.e., >80%) protein bound and characterized by a small therapeutic index. Although the concentration of free drug increases, that of total drug in the plasma tends to decrease because unbound drug is free to distribute into tissue (Ehrnebo et al., 1973). Consequently, drug half-life may increase, and longer dosing intervals may be indicated for potentially toxic drugs. Increased clearance of unbound drug may ultimately "normalize" a half-life that has been lengthened by an increased volume of distribution.

Differences in regional organ blood flow might cause clinically important changes in drug disposition in pediatric animals. Differences in renal blood flow have been documented (Horster et al., 1971; Horster and Valtin, 1971) and result in clinically important differences in drug excretion. Blood flow to vessel-rich tissues of the body (i.e., heart and brain) is greater and faster (Robinson, 1983); the pediatric patient is thus more susceptible to drug-induced cardiac and central nervous system toxicity. The potential for central nervous system toxicity is further increased because the blood-brain barrier is poorly developed immediately after birth. Increased permeability protects the neonatal brain from a deficiency of nutritional fuels in stressful states (e.g., hypoglycemia, hypoxia, and acidosis) by allowing the movement of oxidizable substrates such as lactate into brain cells (Hellmann et al., 1982). Drugs normally incapable of reaching the adult brain are, however, also able to reach brain cells, which are very susceptible to their effects.

Metabolism Drug elimination, including both hepatic metabolism and renal excretion, is limited in neonatal and pediatric patients. Thus, many drugs administered to the young animal are characterized by decreased clearance (Rane and Wilson, 1983; Greene and Mirkin, 1984). In contrast to human infants, hepatic metabolism of drugs is incompetent in the near-term and neonatal puppy (Reiche, 1983; Peters et al., 1971; Inman and Yeary, 1971). Both phase I (e.g., oxidative) and phase II (e.g., glucuronidation) reactions are reduced. The various pathways of metabolism mature at different rates. Phase I activity may not occur in the neonatal puppy and may not be evident until day 9.

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Figure 2–3. The large head that renders pediatric patients so endearing exemplifies the larger component of body weight represented by extracellular fluid in this age group. Increased extracellular fluid and increased total body water increase the volume of distribution of most drugs, thus lowering plasma drug concentrations. The elimination half-lives of most drugs also will increase, suggesting that a longer dosing interval is needed.

Activity appears to progressively increase after day 25, not reaching adult levels until 135 days postpartum (Peters et al., 1971). Generally, decreased hepatic drug metabolism is reflected as decreased plasma clearance, increased plasma half-life, and potentially toxic PDCs. Dose reduction, dose prolongation of intervals, or both may be indicated for some drugs. Oral bioavailability of drugs characterized by significant first-pass metabolism in adults (e.g., propranolol) is probably greater in puppies and kittens. Response to pro-drugs, such as primidone, prednisone, enalapril, and, potentially, methylprednisolone may be reduced because of decreased formation of active drug products. Pediatric hepatic drug metabolizing enzymes do appear to be inducible by phenobarbital and other drugs. Nonhepatic drug metabolizing enzymes also appear to be decreased in pediatric patients. For example, pediatric lower plasma cholinesterase can result in increased sensitivity to organophosphates, succinylcholine, and procaine.

Excretion Reduced renal excretion, characteristic of the pediatric puppy, results in decreased clearance of renally excreted parent drugs and products of phase II drug metabolism. Although the number of glomeruli remains constant throughout pediatric development, both glomerular filtration and renal tubular function progressively increase (Horster and Valtin, 1971; Cowan et al., 1980). Adult values may not be reached until approximately 2.5 months of age. In contrast to glomerular filtration and secretion, renal tubular reabsorption in puppies appears to be similar to that in adults as long as body fluids and electrolytes are maintained (Kleinman, 1978; Bovee et al., 1984). The sequelae of developmental changes in pediatric renal function include decreased clearance and prolonged half-life of drugs (primarily water soluble) excreted by the kidneys. Such a pattern has been shown for several drugs. Compared with current recommendations for adults, pediatric patients may require a higher dose (due to increased volume of distribution) and longer intervals (due to increased distribution and decreased clearance) for gentamicin administration. More importantly, modifications should be anticipated in the gentamicin dosing regimen of unhealthy puppies because they are likely to be affected by conditions that increase the potential for gentamicin-induced nephrotoxicity (e.g., dehydration). However, underdeveloped glomeruli may actually protect the pediatric patient from aminoglycoside-induced nephrotoxicity (Boothe and Tannert, 1991). Further investigations are needed to establish safe yet effective doses of gentamicin for the neonatal puppy or kitten.

Specific Drug Therapy for the Pediatric Patient

Fluid Therapy Pediatric patients are predisposed to dehydration because extracellular fluid is increased, renal capacity to conserve water is decreased, the surface area to body weight ratio is large, and fluid loss through immature skin is greater (Kerner and Sunshine, 1979). Fluid requirements are greater for pediatric patients than for adults. Rates recommended for daily maintenance vary from 60 to 180 mL/kg/day (Mosier, 1981). Pediatric patients cannot accommodate volume overload as efficiently as adults. Although larger fluid amounts are indicated, care must be taken with both the amount and the rate of fluid administration. Fluids can be administered by several routes. Crystalloids administered rectally should be isotonic; rapid rectal absorption of hyperosmolar solutions can lead to life-threatening hyperosmolarity. Subcutaneous administration may be an acceptable route if small volumes of isotonic fluids are administered in patients with normal hydration. Intraosseous fluid administration is an acceptable route of administration if a central vein is not accessible (Otto et al., 1989). Oral rehydration is recommended as the preferred therapy for dehydration caused by diarrhea in human pediatric patients (Hirschhorn, 1982).

Antimicrobial Therapy As for adults, an appreciation of the chemotherapeutic triangle (i.e., relationship between host, drug and microorganism) is necessary for the appropriate use of antimicrobials with pediatric patients. Several antimicrobials should be avoided in pediatric patients. These include chloramphenicol, tetracyclines, doxycycline, and other drugs that undergo enterohepatic circulation (e.g., clindamycin) and thus are more likely to disrupt the normal colonization of the alimentary tract in pediatric patients.

β-Lactam antibiotics are generally the drugs of choice for pediatric patients whenever possible. Although drug half-lives are likely to be prolonged, they tend to be safe because they are characterized by a wide therapeutic index. Higher doses may be necessary to achieve desired peak PDCs because their distribution is greater. Time interval of administration can be prolonged to compensate for the longer half-life. Therapeutic drug monitoring should be used to improve the safety and efficacy of aminoglycosides whenever possible. Higher doses and longer intervals may be necessary to achieve recommended peak and trough concentrations. Amikacin, potentially less nephrotoxic (and more effective against *Pseudomonas* spp.) than gentamicin, should be used whenever possible. Quinolones are very effective and, for most patients, safe antimicrobials. They are characterized by excellent tissue distribution. These drugs should, however, be avoided in large breed pediatric animals because of destructive lesions in the cartilage of long bones. Thus, the author does not recommend these drugs as first choice for any pediatric patient. The combination of a sulfonamide with trimethoprim or ormetroprim tends to be safe and effective for kittens and puppies. Therapeutic indications for lincosamides and macrolides are limited for pediatric patients. Because both groups of drugs undergo extensive biliary secretion and enterohepatic circulation, they should not be used as first-choice antimicrobials. An exception should be made for *Mycoplasma* infections for which tylosin is the drug of choice. Metronidazole is the drug of choice for *Giardia* infections in dogs and cats, and it is often used for the treatment of anaerobic infections. Decreased clearance and prolonged half-life should be anticipated in kittens and puppies; lower doses and longer intervals may be necessary to avoid central nervous system toxicity.

Sedation, Anesthesia, and Analgesia Opioid agonists are the preferred sedative, premedicant, or analgesic of some veterinary clinicians for pediatric patients (Robinson, 1983). Although associated with marked cardiac and respiratory depression, the effects of opioid agonists are largely reversible with opioid antagonists. Bradycardia can be avoided in older pediatric patients by premedication with atropine or glycopyrrolate. Whereas the duration of fentanyl analgesia (nontransdermal patch) is generally too short to justify its use for adult patients, some clinicians prefer it for short-term intraoperative analgesia for pediatric patients because it minimally affects the cardiovascular system. The combination of fentanyl and droperidol has been used with pentobarbital for ear trimming and to induce anesthesia in cardiac patients. Ketamine can be administered subcutaneously, intramuscularly, or intravenously for the restraint and immobilization of young cats. Response to ultrashort barbiturates such as thiopental and methohexital or similar agents (e.g., propofol) should be exaggerated in young animals because of decreased body fat and hepatic clearance. Dilution to a 1% to 2% solution is indicated to prevent overadministration.

Complications associated with intravenous administration can be reduced by rectal administration of either thiopental or methohexital in human pediatric patients. As a class, the benzodiazepines can probably be used safely in pediatric patients. Elimination occurs primarily by hepatic metabolism and is likely to be slower in pediatric patients. Benzodiazepines are, however, characterized by a wide therapeutic index. Midazolam, the newest member of this group, is more potent, has a faster onset of action, and is more rapidly eliminated than diazepam. Although not approved for use in human pediatric patients, it has been used in this age group successfully to induce sedation (Nahata, 1988). Inhalant anesthetics are preferred for maintenance anesthesia in veterinary pediatric patients. Halothane, methoxyflurane, enflurane, and isoflurane have been used. Isoflurane is becoming more popular for pediatric patients because both induction and recovery are rapid and the incidence of adverse effects is less. Hypotension is a complication of all gas anesthetics, however, and variable patient response necessitates close monitoring.

Pregnancy and Lactation

Maternal-Fetal-Placental Unit

Maternal The effects of pregnancy can alter all phases of disposition in the mother. Gastrointestinal motility and gastric acid secretion decrease and may lead to decreased drug absorption. Decreased albumin concentration results in decreased binding of highly protein-bound drugs. Increased volume of distribution of unbound drugs may result in lower PDCs and more rapid drug clearance. Increases in cardiac output, renal blood flow, and glomerular filtration rate can further decrease drug concentrations, particularly of antibiotics. High progesterone concentrations may induce hepatic microsomal enzymes and increase drug metabolism (Papich and Davis, 1986).

Fetus and Neonate Unique differences in drug disposition predispose the near-term fetus and neonate to adverse drug reactions. The idea of absolute placental selectivity has been replaced with the realization that essentially all drugs administered to a pregnant animal are transferred across the placenta, regardless of the degree of intimacy between fetal and placental membranes (Welsch, 1982; Levy, 1981). The responses of the fetus and newborn to individual drugs, however, vary. Differences in responses reflect, in part, differences in placental kinetics of drugs. Current efforts in human neonatology are concerned with the characterization of the pharmacokinetic differences between drugs in the near-term fetus. Even the most simple pharmacokinetic representation of the maternal-fetal system is, however, complex, being composed of at least three compartments: maternal, placental, and fetal. The pharmacokinetics of each compartment is determined, in turn, by its own rate of absorption, distribution, metabolism, and elimination (Levy, 1981; Welsch, 1982; Krauer and Krauer, 1991). Furthermore, pregnancy is a dynamic state characterized by dramatic changes in placental and fetal growth and in the physiology of the pregnant animal. All pharmacokinetic processes change in concert with the progression of pregnancy. Species differences in placental drug transfer do exist, making extrapolation of information to small animals difficult. The route of administration is also likely to determine the amount of placental transfer: Routes that result in higher plasma peak concentrations (i.e., intravenously, as an intravenous infusion, and in multiple doses) are likely to expose the fetus to higher drug concentrations.

Although many factors determine the rate and extent of drug transfer across the placenta, the lipid solubility of the drug and a steep maternal-fetal drug concentration gradient are probably the most important (Welsch, 1982). In general, non-ionized compounds with high lipid solubility cross rapidly, whereas drugs with little lipid solubility cross slowly. Impermeability of the placenta to polar compounds, which generally do not penetrate cell membranes, has been described as relative rather than absolute (Welsch, 1982). A number of drugs that are polar at physiologic pH can cross the placenta rapidly (Welsch, 1982). Occasionally, placental metabolism may reduce the concentration of selected drugs reaching the fetal umbilical vein.

Differences in drug disposition compared with both pediatric animals and adults can lead to adverse reactions in the near-term fetus receiving drugs through the placenta. Fetal protein is generally less in the neonate, which is, in turn, less than that in the adult (Levy, 1981; Welsch, 1982). Thus, higher concentrations of unbound and pharmacologically active drugs can be anticipated. Perhaps more important are anatomical peculiarities of fetal circulation. Because the fetal liver and lungs are largely bypassed, blood reaching the heart and brain contain essentially the same concentration of drugs as present in the umbilical vein. Although fetal metabolism of drugs can contribute to the ultimate elimination of drugs in the human neonate, the amount of drug metabolizing enzymes present in near-term animals is negligible (Welsch, 1982).

Although drugs administered to pregnant animals may be detectable in the fetus, they may not produce clinically important effects. Examples of drugs that have been shown to reach detectable and potentially clinically important concentrations in the fetus include salicylates and other NSAIDs, anticonvulsants (phenytoin and diazepam), local anesthetics such as lidocaine, gentamicin (in some species), and narcotic analgesics. In human infants, the ratio of maternal to fetal concentration of β-lactams approximates 1 (Nau, 1987). Because predicting the effects of a drug crossing the placenta is difficult, drug selection for the mother should be based, in part, on anticipated safety to the near-term fetus.

Lactation As is the fetus, the nursing animal is an inadvertent recipient of drugs administered to the mother. Most of the pertinent information in the veterinary literature is concerned with excretion of drugs in the milk of food animals; there appears to be no information regarding small animals. Studies of humans indicate that drugs diffuse into the milk from maternal circulation. Low molecular weight (<200), un-ionized, highly lipid-soluble drugs that are minimally protein bound diffuse into the lactating mammary gland rapidly, whereas water-soluble drugs diffuse more slowly (Berlin, 1981). The pK_a of a drug largely determines its concentration in milk. Animal milk tends to be acidic compared with plasma pH. Thus, although a drug may be non-ionized in the plasma, and thus more likely to diffuse into milk, it may become ionized and nondiffusible once in the milk. Such "ion trapping" can concentrate drugs in milk. The ratio of drugs in milk to plasma is predictable, being greater for weak bases and weak acids whose pK_as differ from the pH of milk by 2 pH units (+2 for acids and −2 for bases) (Rasmussen, 1979). Generally, the amount of drugs excreted in milk is less than 2% of the maternal dose (Berlin, 1981). Greater concentrations can be expected, however, if a drug is administered to the mother intravenously, as an intravenous infusion, or in multiple doses.

Not all drugs ingested with milk during nursing will be absorbed from the gastrointestinal tract of the nursing animal. For example, milk may decrease the absorption of some drugs, whereas the pharmacokinetic properties of other drugs (i.e., aminoglycosides) preclude their absorption except in the very young. Not all drugs, however, must be absorbed to cause clinically important adverse effects. For example, antimicrobials can potentially alter the developing flora of the pediatric alimentary tract (Jones, 1987; Smith, 1965). Thus, it is prudent to avoid administration of potentially toxic drugs to the lactating bitch or queen.

Roles of Species and Breed Differences in Drug Disposition

Species that are physiologically similar tend to have similar drug disposition patterns, and the same dosing regimen can often be used for a particular drug (Vessey, 1982). Thus, dosing regimens recommended for the dog frequently can be extrapolated to the cat. Extrapolating human dosing regimens to the dog can be problematic, particularly since human doses are often not based on a per kilogram basis. Unfortunately, despite the fact that drugs approved for use in humans are firstly studied in dogs, data regarding comparisons is not generally available. Drug therapy in dogs and cats with drugs labeled for human use often reflect extrapolation of dosing regimens used in human patients. Further, drug use in cats often reflects extrapolation of dosing regimens used in dogs. Only occasionally is a scientific basis for extrapolation of a human drug available. An appreciation of physiologic differences can increase the likelihood of success in extrapolation of dosing regimens to or between dogs or cats (Boothe, 1990; Boothe and Tannert, 1991; Wilcke, 1984; Baggott, 1977).

Absorption

The rate and magnitude of drug absorption for most drugs appear to be similar for both the dog and cat, regardless of the route of administration. An exception may need to be made for slow-release preparations; rates and extent of absorption do vary among species. Because slow-release preparations used in human patients are designed to maintain therapeutic concentrations in humans, absorption kinetics of these products can be profoundly different in the dog and cat. Use of such drugs should be based on clinical studies of these preparations in dogs and cats.

Distribution

Although differences in drug distribution between the species tend to be minor, they can result in important differences in drug response. Blood volume of the cat (70 mL/kg) is less than that of the dog (90 mL/kg); PDCs of drugs whose distribution is confined to the plasma compartment may therefore differ between the species. The same amount of drug (on a per kilogram basis) is diluted less in cats because the plasma volume is smaller. Thus, drug concentrations after administration of a milligram per kilogram dose might initially be higher in cats than in dogs. Organs that are well perfused (i.e., heart, brain) may be more susceptible to toxicity. Cats are approximately the same size as the smaller dog breeds. Thus, doses determined for medium-sized to large-sized dogs may not be appropriate for the cat because the smaller animals have a greater body surface area. In larger animals, body water comprises a larger proportion of body weight, which tends to dilute out the drug. A higher dose may be needed for larger animals. Because the drug half-life may be longer (due to increased distribution), however, the dosing interval may need to be longer.

Differences in plasma protein-binding characteristics (particularly albumin) may alter the distribution of drugs that are highly protein bound. The degree to which various drugs are protein bound varies dramatically among the species. For a drug highly protein bound, a difference of 10% in binding can be disastrous in some patients. Although the elimination characteristics of many drugs have been established for cats, few studies have determined the extent of protein binding.

The effects of disease can markedly alter distribution. The unhealthy cat does not maintain hydration as well as the dog; fluid imbalances resulting from dehydration or edema alter drug distribution. The obese cat can represent a "sink" for drugs that are lipid soluble, thus lowering PDCs potentially to submaximal levels if the dose is not appropriately increased. Weight loss in a hyperthyroid cat can have the opposite effect.

Metabolism

The most significant and best characterized differences in drug disposition between the dog and cat probably result from differences in drug metabolism. Identification of phase I enzymes and their specific drug substrates is difficult, and few species differences have been described in the cat or dog. Deficiencies in demethylation and hydroxylation have been described in the cat and may be responsible for different patterns of pro-drug activation (e.g., primidone; see Chapter 24) or adverse reactions to selected drugs (i.e., chloramphenicol) (Watson, 1978). The recently described reaction of cats to diazepam may represent differences in the metabolites produced, as may the susceptibility of the feline liver to metabolite-induced damage (Elston et al., 1993).

Differences in phase II enzymes and their drug substrates have been better identified and account for many of the differences in drug disposition between the dog and cat (Baggott, 1977). Most of these differences result from a deficiency of glucuronide conjugation in the cat. The deficiency reflects extremely low concentrations of some glucuronyl transferases. Thus, many drugs excreted as glucuronide conjugates in other species are characterized by a prolonged clearance rate and half-life in the cat. Toxic levels may accumulate much faster in the cat, and exaggerated pharmacologic responses or toxicities occur more easily. Dosing regimens must be modified for such drugs by either decreasing the dose (especially for drugs whose dosing interval is shorter than the elimination half-life) or prolonging the dosing interval. For example, the half-life of aspirin approximates 36 hours in cats compared with 8 hours in dogs. To avoid toxicity in the cat, aspirin is dosed every 48 to 72 hours compared with twice daily in dogs. Acetaminophen is toxic in the cat because it is not glucuronidated sufficiently fast. Excessive acetaminophen is shunted to phase I enzymes, resulting in the production of toxic metabolites. The toxic metabolites overwhelm the glutathione scavenging system of feline erythrocytes and hepatocytes, resulting in life-threatening methemoglobinemia and (potentially) hepatic necrosis. Cimetidine can be helpful for cats reacting adversely to acetaminophen (if administered within 48 hours) because it inhibits phase I drug metabolizing enzymes.

Not all drugs that are conjugated with glucuronide are predisposed to toxicity in the cat. This is true for several reasons. First, the cat is deficient only in certain families of glucuronyl transferase. Cats can conjugate and excrete endogenous substrates such as bilirubin, thyroxine, and steroid hormones as well as other species. Metabolism of a variety of exogenous drugs, however, particularly phenols and aromatic acids and amines, occurs at a much slower rate in the cat than in other species (Baggott, 1977; Welch et al., 1966). The degrees of deficiency and potential toxicity depend on the drug substrate. For example, some phenolic compounds are sufficiently conjugated, whereas others are not. Second, glucuronide-conjugated drugs characterized by a wide safety margin are associated with few adverse reactions even if accumulation occurs. Finally, in the absence of glucuronide, drugs may be sufficiently metabolized by an alternative pathway. Some sulfates may be particularly well developed in the cat, and many drugs that are excreted as glucuronide-conjugates by the dog may be excreted as sulfated compounds by the cat. Other sulfate-conjugating systems, however, appear to be easily saturated in the cat. Unfortunately, alternate pathways of drug metabolism may also contribute to the toxicity of some drugs (e.g., acetaminophen) because they may involve phase I enzymes that catalyze the formation of toxic metabolites. Thus, drugs shunted to another pathway in the cat may be very toxic to the cat but minimally toxic in other species.

With the exception of acetylation, deficiencies in phase II enzyme activity have not been described in the dog. Acetylation is not a common route of elimination for drugs, and the clinical significance of this deficiency is not well known. An exception can be made for the antiarrhythmic procainamide. The drug is acetylated in humans to an active metabolite. Procainamide is less potent in dogs presumably because of the lack of the active acetylated metabolite. Thus, a higher dose must be given to dogs (compared with humans) to achieve an equivalent pharmacologic response.

Renal Excretion

In contrast to hepatic metabolism, differences in renal excretion between the dog and cat do not appear to be profoundly important to drug disposition. The glomerular filtration rate of cats (2.5 to 3.5 mL/min/kg) is less than that of dogs (3 to 5 mL/min/kg), suggesting that renal clearance of drugs may be faster in dogs. Although this is true of inulin, differences have not been established for most drugs. Renal disease profoundly alters the rate of drug excretion in all species. In general, serum creatinine concentrations can be used to modify the dose (decrease in proportion) or interval (prolong in proportion to abnormality). The modification should be applied only to that portion of the drug eliminated by the kidney. Note that fluid imbalances in renal disease can also alter drug distribution.

Role of Species Differences in Target Tissues

It is difficult to predict differences in drug reaction that can be ascribed to differences in target tissues because very little is known about cats. Differences in response to selected drugs (e.g., opioids, insulin, chlorinated hydrocarbons) are known to be or are thought to be reflections of differences in tissues.

Feline erythrocytes (hemoglobin) appear to be more susceptible to oxidation and thus to methemoglobinemia. Drugs reported to cause methemoglobinemia in the cat include urinary antiseptics containing methylene blue (Shecter et al., 1983) or azodyes, acetaminophen (Cullison, 1984; Welch et al., 1966; Savides et al., 1985) and related compounds, benzocaine (Wilkie and Kirby, 1988) and propylthiouracil (Peterson et al., 1984). Several mechanisms have been postulated to explain the potential increased sensitivity of cats to methemoglobin formation. Lower concentrations or activities of the intracellular repair enzyme methemoglobin reductase have been postulated but not confirmed (Stolk, 1966; Boothe, 1990a). Faster metabolism of specific drugs to toxic metabolites is a likely cause for some drugs, particularly those whose elimination is shunted to alternate (toxic) pathways (i.e., acetaminophen) (Cullison, 1984). Differences in the structure of feline hemoglobin have also been postulated. Feline hemoglobin contains up to 20 sulfhydryl groups compared with a maximum of 4 in other species. Sulfhydryl groups tend to be reactive and thus are susceptible to interaction with reactive parent drugs or metabolites. Thus, more sulfhydryl groups would need to be maintained in a reduced state in cats (Harvey and Kaneko, 1976).

Another possible mechanism of increased methemoglobin formation in the cat might be differences in intracellular levels of glutathione conjugating enzymes. Because these enzymes scavenge reactive products that might oxidize sulfhydryl groups, a relative deficiency could predispose the cat to hemoglobin oxidation. The role of intracellular levels or activity of glutathione conjugating systems of the feline erythrocyte in methemoglobinemia has not been addressed. Because the cat responds favorably to glutathione precursor supplementation (e.g., *N*-acetylcysteine) after acetaminophen toxicity, however, differences in the activity of this system might also be important and need to be investigated.

Breed Differences

Breed differences exist in drug disposition, although they have not been well described. In humans, subpopulations of "poor hepatic metabolizers" of certain drugs have been identified as being predisposed to adverse drug reactions because of a relative "overdose." A similar difference in drug dispositions should be anticipated in both dogs and cats. Sighthounds (e.g., Salukis, greyhounds; Fig. 2–4) offer an example of breed differences in drug disposition. Their lean body weight provides little fat tissue for drug distribution. As a result, they are more susceptible to overdosing with drugs that redistribute (rapid movement of drug into a body compartment such as the brain, followed by slower movement into other compartments such as fat) such as thiobarbiturates. Brachycephalic breeds are more susceptible to cardiac arrhythmias (sinoatrial block) caused by acepromazine. Beagles offer a different consideration. Many drug studies have used the beagle as a model for drug disposition. Yet, purpose-bred beagles have been so well specialized for research that they are not necessarily representative of the general population of dogs, and thus extrapolation of drug studies between this breed and dogs in general must be done cautiously. Breed differences in drug disposition should be expected in both dogs and cats and warrant further studies.

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Figure 2–4. Sight hounds as represented by the greyhound are a breed that is recognized to handle drugs differently. The small amount of body fat contributes to differences in response to anesthetic agents that undergo redistribution. Differences in metabolism may exist.

Miscellaneous

Differences in circadian rhythm (i.e., diurnal vs. nocturnal) play a role in some differences between the dog and cat. Aminoglycosides are less likely to cause toxicity if administered during active periods. This has been established for theophylline, for which clearance occurs more rapidly at night in the dog compared with early morning in cats. Dosing of glucocorticoids at night has been recommended for cats in order to mimic endogenous release patterns. The clinical significance of these differences has not been determined.

RECOMMENDATIONS REGARDING EXTRAPOLATION OF DOSING REGIMENS

Drug Information Sources

Extrapolation of doses of human drugs to dogs and cats and from dogs to cats should be based on a knowledge of the clinical pharmacology of the drug to be administered and on the physiologic differences of the target species. The safer the drug, the safer the extrapolation. Numerous resources are available for human drug information (*Physicians' Desk Reference, Facts and Comparisons, USP Pharmacopeia*, the package insert from the product) to determine the safety and the determinants of disposition of a new drug. Several sources are now available on the Internet (see Appendix 7). The veterinary literature and clinicians with expertise in the field, including diplomates of the American College of Veterinary Clinical Pharmacology, are additional sources.

Note that every drug that has been approved for use in humans has been studied in dogs. The studies have focused on *safety*, however, not efficacy. The information regarding safety (often including pertinent pharmacokinetic data, such as volume of distribution, bioavailability, and drug elimination half-life) may be obtainable through a *Freedom of Information* request, which would be processed by the FDA (Freedom of Information Staff [HFI-36], 5600 Fishers Lane, Rockville, MD 20857; (fax 301-443-1726).

Extrapolation of dosing regimens should be limited to relatively healthy animals, if possible, to avoid the effects of disease on drug disposition. Likewise, extrapolation to geriatric and pediatric patients should be avoided. Administration by the oral route is generally safer (although gastric irritation may be more likely). Oral administration is less preferred if the drug undergoes first-pass metabolism, however, because this can vary dramatically among animals. A 50% change in first-pass metabolism may double the pharmacologically active dose in a patient. Intravenous administration should be avoided; when it is unavoidable, the drug should be administered slowly (over 5 to 10 minutes or more). Drugs with long half-lives (>12 hours) should generally be avoided. If a drug is administered at an interval that is less than the drug half-life, accumulation should be anticipated and accounted for in the dosing extrapolation. Note that maximum adverse effects may not appear until accumulation is complete at steady state. Also, a drug half-life can change (due to disease or drug interactions). Thus, a drug that initially did not accumulate (and whose dose is based primarily on volume of distribution) may begin to accumulate as disease worsens. Unless the drug can be monitored, a change in drug half-life will be missed. In such instances, a dosage reduction is again indicated. On the other hand, as a patient improves, response to therapy may again change disposition, perhaps leading to therapeutic failure. One should be prepared to treat adverse effects if they occur. If the drug half-life is long, the time necessary for abatement of the adverse reaction will also be long. In general, extrapolation of lipid-soluble drugs should be avoided because of the risk of too many species differences.

Water-Soluble Drugs

As a general rule, extrapolation of doses for drugs that are water soluble is more appropriate because these drugs are distributed to extracellular fluids (normalizing volume of distribution); protein binding is likely to be negligible; and hepatic metabolism is minimized. Drug volume of distribution and renal elimination may be similar among species, and the interval used for such drugs can often be extrapolated among species. The dose administered, however, probably should be reduced to compensate for differences in blood volume among animals. Increased doses are indicated for pediatric patients and for patients with edema; decreased doses are indicated for geriatric and dehydrated patients.

Lipid-Soluble Drugs

Lipid soluble drugs tend to be distributed to total body water and beyond, leading to a greater risk of differences among species. They are more likely to be highly protein bound, leading to a risk of differences in tissue distribution and in the proportion of pharmacologically active drug. In contrast to water-soluble drugs, lipid-soluble drugs are more likely to require hepatic metabolism. In general, anticipate a longer half-life in cats for drugs that undergo phase I metabolism in other species. Note that species differences in phase I metabolism can be very profound. If acetylation is a major phase II route of elimination, it is likely that the drug may be metabolized faster in cats than in dogs. If phase I metabolism and glucuronidation is the major route of elimination, a longer half-life should be anticipated in cats. Although glucuronidation does not necessarily indicate that elimination of the drug will be slower in cats, until an appropriate study has established the kinetics of the drug in cats, its use should be avoided. An exception might be made if the drug can be monitored or the drug is characterized by a wide therapeutic window. Slow-release preparations should be avoided because rates of absorption among the species can be dramatic. Finally, preparations containing propylene glycol and other unknown carriers might need to be avoided because of adverse reactions in cats.

All Drugs

Drugs with large (>2 L/kg) volumes of distribution should be avoided because this indicates that accumulation or tissue binding of the drug may occur. These factors are likely to vary among species. Pro-drugs and slow-release drugs should be avoided because the amount of active drug is not predictable among the species. Body surface area should be used whenever possible to determine doses of toxic drugs. Drug disposition may change as the animal improves, particularly if a disease that affects drug disposition (i.e., cardiac, renal, hepatic) is being treated. Changes in dosing regimen may again be indicated. Finally, one should be aware of the laws regulating the use of human-labeled drugs.

Compounding

A major problem with extrapolating doses in animals occurs with preparations formulated for humans: the size of the tablet often precludes accurate dosing. Note that several pharmacies in the United States now cater specifically to veterinarians and thus are prepared to address such problems. In addition, carrier agents or fillers can be purchased commercially and used to dilute drugs to more usable sizes. Compounding is discussed further in the Appendix.

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Drug-Induced Diseases

3

Dawn Merton Boothe*

INTRODUCTION
PRINCIPLES OF TOXICOLOGY: DEFINITIONS AND TERMINOLOGY
ALLERGIC DRUG REACTIONS
LIVER
HEPATOTOXIC DRUGS
Glucocorticoids
Inhalant Anesthetics
Anticonvulsive Therapy
Acetaminophen and Other Analgesics
Mebendazole and Oxibendazole
Sulfonamides
Thiacetarsamide
Bile Acids
KIDNEY
NEPHROTOXIC DRUGS
Aminoglycosides
Nonsteroidal Anti-inflammatory Drugs
Angiotensin-Converting Enzyme Inhibitors
Amphotericin B
Other Drugs
GASTROINTESTINAL
CENTRAL NERVOUS SYSTEM
OTOTOXICITY
INTEGUMENT
ENDOCRINE SYSTEM
HEMATOLOGIC DYSCRASIAS
PULMONARY TOXICITY
MISCELLANEOUS DISORDERS
AVOIDING TOXIC REACTIONS
REPORTING ADVERSE DRUG REACTIONS
CLINICAL LABORATORY TESTS

INTRODUCTION

An adverse drug reaction is any undesirable reaction to therapy with a drug. Adverse drug reactions can be classified as type A or type B (Lawson and Richard, 1982; Griffin and D'Arcy, 1979). Type A ("augmented") adverse reactions generally result from plasma drug concentrations (PDCs) that exceed the maximum therapeutic range or, less commonly, drop below the therapeutic range (see Chapter 1). If the clinician is familiar with the drug and the patient, type A reactions are largely predictable. Generally, they are manifested as an exaggerated, but normal or expected pharmacologic response (Fig. 3–1). This response might, however, be the primary or desired response (e.g., bradycardia in a patient receiving propranolol to slow a sinus tachycardia). Alternatively, the reaction might be an unwanted, secondary response resulting from the drug's pharmacologic effects (e.g., bronchospasms induced by the β-blockade effects of propranolol). A reduced response to a drug because therapeutic drug concentrations were not reached (i.e., underdosing) is a variation of a type A adverse reaction (Fig. 3–2). Some drugs also cause adverse reactions unrelated to their pharmacologic response. These reactions usually reflect damage to target cells and are referred to in this chapter as *cytotoxic adverse reactions.* Cytotoxic adverse reactions are perhaps best exemplified by hepatic necrosis or methemoglobinemia induced by acetaminophen. Often it is the metabolite of the drug rather than the drug itself that causes cytotoxicity. In such cases, drugs that induce metabolism, particularly in the liver (e.g., phenobarbital, phenytoin; Fig. 3–3), may increase the risk of toxicity, whereas drugs that decrease metabolism reduce the risk of toxicity (e.g., cimetidine) (Ariens et al., 1976; Mitchell et al., 1984; Klassen, 1985). Cytotoxic drug reactions might be treated with drugs that scavenge radical metabolites (i.e., *N*-acetylcysteine, a glutathione precursor).

In contrast to type A reactions, type B ("bizarre") reactions are not dose or concentration dependent. As a result, these reactions are not predictable and are largely unavoidable. They occur only in a small percentage of the population receiving the drug. Generally, their incidence—indeed their existence—often is not documented until the drug is in wide use. In addition, because their cause is not well understood, treatment is generally limited to symptomatic therapy. Examples of type B adverse reactions include drug allergies or idiosyncrasies. Many of these adverse reactions ultimately may be shown to be genetically or otherwise based, but the cause has yet to be identified and thus the reaction cannot be predicted. As with type A reactions, type B reactions can occur in response to the parent drug or its metabolite.

This chapter discusses the mechanisms and clinical signs of the adverse reactions caused by selected drugs and methods by which the reactions might be avoided or treated. Adverse reactions that result from the expected pharmacologic action of a drug (i.e., exaggerated pharmacologic effect) are discussed with each drug in subsequent chapters and are not emphasized here. Cytotoxic reactions and the occasional secondary adverse reactions are often unexpected and not recognized. This chapter focuses on type A adverse reactions. Type B reactions are also discussed when known. The list of drugs discussed is by no means intended to be complete but represents those drugs most commonly recognized as well as the addition of some that are often overlooked.

A variety of factors can influence the likelihood of adverse, and particularly toxic, reactions (Ariens et al., 1976; Mitchell et al., 1984; Klassen, 1985). Factors that predispose a patient to the development of type A adverse reactions are discussed in Chapter 2. Further discussion of

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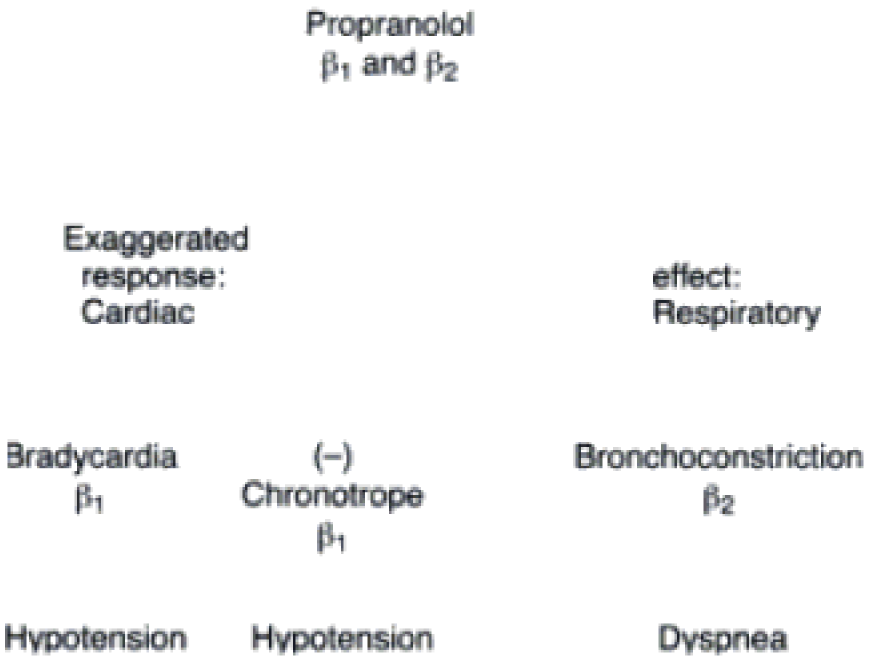

Figure 3–1. Type A drug reactions due to overdose. Propranolol offers an example of a type A adverse reaction that reflects both an exaggerated primary response (bradycardia, decreased contractility) and an undesirable secondary response (bronchospasm).

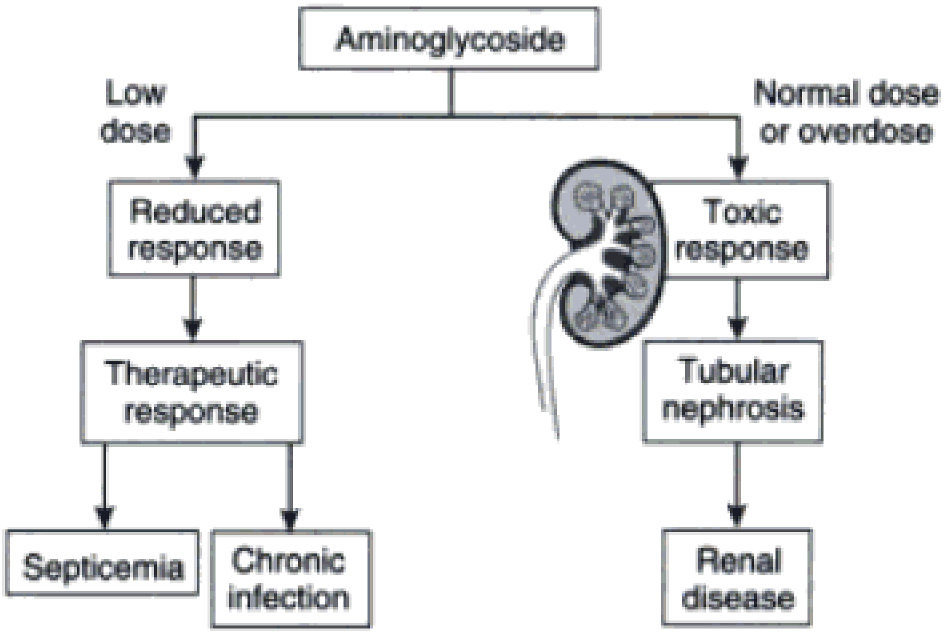

Figure 3–2. An aminoglycoside such as gentamicin can cause two examples of a type A adverse reaction, reflecting therapeutic failure should effective antimicrobial concentrations fail to be achieved, and a cytotoxic reaction, manifested as nephrotoxicity in response to persistent (but not necessarily markedly increased) plasma drug concentrations.

each drug or drugs not addressed in this chapter can be found in the specific chapter that discusses the therapeutic use of the drug. Note that alternative health agents (e.g., herbal remedies, nutraceuticals) and over-the-counter products can also cause adverse reactions. Despite being referred to as "natural," many herbal remedies and health food products contain drugs. These products may not be regulated in veterinary medicine, and neither safety nor efficacy may have been established.

The organs most susceptible to type A drug reactions usually are those subjected to the greatest exposure or concentration of the drug. Thus, the organs with the greatest blood flow and those organs capable of drug concentration, such as the liver and kidney, are the most vulnerable to systemic drugs. Highly metabolically active organs are also more likely to manifest toxic effects for two reasons. First, such organs depend on the presence of energy, and anything that impairs acquisition of energy (including blood flow) can lead to malfunction. Second, if the metabolic activity includes metabolism of compounds, the production of potentially reactive metabolites can increase the likelihood of cytotoxicity if these metabolites interact with cellular structures. The organs most susceptible to damage by type B reactions tend to be the organs that contain tissues that act as haptens for drug-induced allergy (e.g., skin, blood-forming units) or tissues that filter and trap immune complexes (e.g., glomerulus and joints). A summary of compounds causing predominantly type A drug reactions and, when available, their antidotes, can be found in Appendix 5.

Not all adverse reactions are clinically relevant. Sometimes the reaction is not detectable unless actively sought. For example, clinical laboratory tests may detect a drug-induced hepatotoxicity (e.g., increased serum alanine transferase activity) that was clinically silent. Many drugs can alter clinical laboratory tests, including endocrine function testing (Young, 1990) (see later discussion of the endocrine and clinical laboratory tests). If an adverse drug reaction is suspected, the importance of reporting the reaction (or suspicion) cannot be overemphasized (see later discussion).

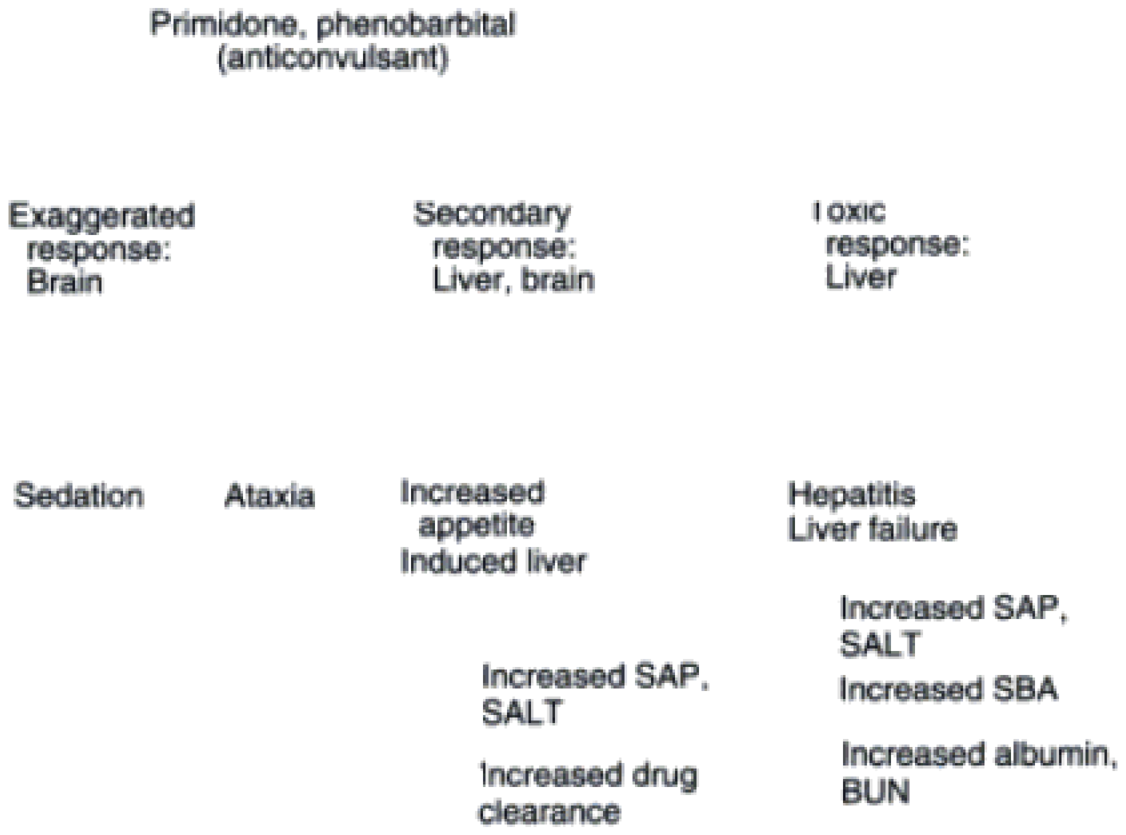

Figure 3–3. Exaggerated and cytotoxic responses. Anticonvulsants metabolized by the liver exemplify a type A adverse reaction manifested as cytotoxicity (hepatic disease). These drugs also can cause an exaggerated (but expected) response (sedation) as well as a secondary undesirable response (increased appetite, polyuria, and polydypsia). BUN = blood urea nitrogen; SALT = serum alanine aminotransferase; SAP = serum alkaline phosphatase; SBA = serum bile acid.

PRINCIPLES OF TOXICOLOGY: DEFINITIONS AND TERMINOLOGY

A *poison* is any substance that is injurious to animals and is synonymous with toxic substance, toxic chemical, and toxicant. It is important to note that any drug can become a poison ("the dose makes the poison"), and the toxic response to the poison tends to correlate with the dose (or duration). A *toxic response* or *toxicity* refers to the effects manifested by an organism in response to a toxic substance. *Acute* toxicity generally occurs from a single dose or exposure. Most acute toxicants rapidly interfere with critical cellular processes. *Subacute* toxicity or *subchronic* toxicity occurs after several weeks to months of exposure. *Chronic* toxicity occurs after months to years of exposure. These latter terms are generally applied to humans but the relative duration of exposure equally applies to animals. Toxic chemicals can act *directly* by injuring the cells with which they come in contact or *indirectly* by injuring a group of cells that subsequently precipitate injury to others. Alternatively, toxins can act indirectly by interfering with a physiologic process on which a group of cells are vitally dependent. Most toxins act systemically, whereas others (such as acids and bases) act locally. Some toxic effects reflect a combination of local and systemic effects (Sipes and Dart, 1998). A less commonly used indicator of the assessment of toxicity is the *LD_{50}*, the dose of a chemical that kills 50% of animals receiving it. Unfortunately, information related to the LD_{50} of a drug may be pertinent only to the laboratory species in which the LD_{50} was established. Current indicators of toxicity in humans more commonly focus on the dose-response relationship as it impacts biochemical and physiologic changes leading to adversity (Sipes and Dart, 1998).

A *teratogen* is a compound that causes abnormal fetal development. It is important to note that teratogenicity is not the only form of toxicity that may occur in utero; any toxic effect that occurs in the adult is likely to occur in the developing fetus as well. *Carcinogenesis* refers to the ability of a compound, or a *carcinogen*, to cause cancer. Cancer cells are cells that have been able to avoid the sophisticated mechanisms that control normal growth, development, and division. Induction of cancer by a compound involves many variables, including duration, dose, and frequency of exposure. Generally, carcinogens take 20 years or more to induce cancer, and the cause and effect relationship between the compound and the cancer often is not recognized. Induction of cancer is divided into three major steps: *initiation* (conversion of the normal cell into a neoplastic cell), *promotion*, and *progression* (Sipes and Dart, 1998). Although some compounds can directly interact with DNA, leading to a cancerous cell, most compounds must first be converted to a reactive metabolite in order to covalently bond with DNA. Damage may still be avoided if DNA repair occurs before cell division. Cellular damage increases the stimulus for division of adjacent cells, leading to a new cell type with new genotypic and phenotypic properties that can then be transformed to a malignant cell under the correct conditions. A number of compounds are recognized to be *initiating agents*, targeting molecular DNA, whereas others are considered *promoters*, acting to increase the incidence of cancer or decrease the latency period without interacting with DNA. These latter compounds must be administered repeatedly and after the initial insult. Endogenous compounds such as growth factors or hormones may act as promoters (Sipes and Dart, 1998).

Many compounds can induce cancer in laboratory animals when they are exposed to extremely high (nontherapeutic) doses for prolonged periods of time. Rarely do these compounds cause cancer in humans, and it is even more unlikely that they will do so in companion animals, in part because their life expectancy is shorter than that of humans. Lifestyle changes that increase the risk of drug or toxicant-induced cancer in humans are likely to have the same effect in animals as well: exposure to cigarette smoke, exposure to charcoal-cooked food, chronic consumption of alcohol (hopefully not in animals), and consumption of "natural" foods, many of which contain possible carcinogens.

ALLERGIC DRUG REACTIONS

The clinical manifestations of allergic drug reactions vary with the type of reaction and the body system targeted. Previous exposure to the drug must occur regardless of the type of reaction, or therapy must have been sufficiently long (i.e., 10 to 14 days) for an allergic response to develop. Drugs generally are too small in size to be sufficiently antigenic. Rather, drugs generally act as haptens, covalently combining with a body tissue that then becomes antigenic. As a result, the allergic response may be directed toward the drug or tissue.

Type I reactions (immediate or anaphylactic) are IgE mediated and result from the release of chemical mediators (e.g., histamine, serotonin, eicosanoids) released from tissue mast cells or basophils. The reaction occurs within minutes after drug administration and regardless of the dose administered. Clinical manifestations generally include nausea, vomiting, circulatory collapse, tachycardia, pulmonary edema, and neurologic signs. Urticaria and angioedema may also be evident. Clinical signs may be species dependent, depending on the "shock" organ of the species. The shock organ generally is the organ in which mast cells occur in greater numbers. In the dog, the shock organ tends to be the liver and gastrointestinal tract; in the cat, the shock organ generally is the lung.

Sometimes the exact antigen that causes anaphylaxis is not known. Anaphylaxis in microfilaremic dogs after administration of microfilaricides is well documented. The specific antigen released by the effect of the drug is not known, however, although the role of microfilaria is generally recognized (Kitoh et al., 1994). When given to microfilaremic dogs, both dimethylcarbamazine and ivermectin can induce shock manifested as peripheral vascular collapse, dyspnea, bloody diarrhea, and other clinical signs and laboratory test results consistent with anaphylaxis.

Treatment of drug-induced anaphylaxis is directed toward prevention of the physiologic response to mediator release (i.e., epinephrine and antihistamines) and prevention of further histamine release (e.g., epinephrine and glucocorticoids; possibly antihistamines). Supportive therapy is also indicated. Treatment on a preventive basis helps decrease the manifestations of anaphylaxis by decreasing the mast cell response. Drugs associated with type I allergic reaction in people include penicillins, angiotensin-converting enzyme inhibitors (particulary in the first 3 weeks of therapy), nonsteroidal anti-inflammatories drugs (NSAIDs), and opioids.

Some drugs can cause an anaphylactic-like reaction (anaphylactoid) that is very similar to anaphylaxis but is not mediated by IgE (i.e., is not allergic or immune mediated). Selected drugs can cause direct mast cell degranulation. Generally these drugs are cationic (basic) and include opioids (particularly morphine), polymyxin, radiographic contrast materials, thiacetarsamide, and amphotericin B. Hyperosmolar solutions such as mannitol can also cause direct mast cell degranulation. Anaphylactoid reactions tend to be related to dose, and administration of a small test dose may help detect the likelihood of occurrence. Decreasing the rate of drug administration as well as previously described prophylactic measures also are indicated.

Type II reactions (cytotoxic) occur as antibody-bound blood cells become lysed and removed from circulation. Lysis occurs due to direct binding by either IgG or IgM. Complement may or may not be activated. Either stem cells in the bone marrow or mature circulating cells may be targeted. Red blood cells, leukocytes, and platelets may be targeted, resulting in hemolytic anemia, agranulocytosis and leukopenia, thrombocytopenia, or any combination thereof.

Type III drug reactions (immune complex disease, or serum sickness) is induced by antigen-antibody complexes involving either IgG or IgM and complement activation. Circulating antigen-antibody complexes may be filtered by and lodged in the vasculature of a number of organs, including the kidney, central nervous system (CNS), or peripheral vasculature. Clinical signs generally refer to the predominant organ affected but also include fever and lymphadenopathy. The Arthus reaction is a variation of the type III reaction and is manifested as swelling and pain at the site of drug administration. Among drug reactions in veterinary medicine, the potentiated sulfonamides are probably the most well-recognized cause of type III immune-mediated drug reaction (Cribb, 1996).

Type IV drug reactions (delayed hypersensitivity, cell mediated) reflect cellular response at the site of the antigen. Lymphocytes and macrophages infiltrate the site and cause mediator release that perpetuates the inflammatory response.

The list of drugs that cause each type of drug-induced allergy is long and probably will remain incomplete. Although some drugs are more likely to cause an allergy, it is probable that any drug can cause any type of allergy. Any body system may be affected. Diagnosing an allergic (or any adverse) drug reaction can be very difficult and generally requires de-challenge (i.e., removal of the drug) and rechallenge. The ethics of rechallenge (i.e., risk to the patient) may not justify confirmation of a presumed diagnosis. When possible, adverse drug reactions in each of the body systems that have an allergic basis should be noted as such.

Drug-induced allergy can be life threatening. Vasculitis and serum sickness are more likely to become life threatening when the kidney, liver, gastrointestinal tract, and nervous system become involved. Angioedema is life threatening if mucosal edema threatens ventilation.

LIVER

The liver is vulnerable to drug-induced toxicity for several reasons (Ockner, 1982; Plaa, 1985; Lee, 1993; Bunch, 1993):

1. It receives a large portion of the cardiac output and thus is exposed to large amounts of drug.
2. The liver is a "portal of entry" for and is exposed to the greatest concentrations of orally administered drugs.
3. The liver is the major site of metabolite formation. Thus, the liver not only concentrates parent drugs but also is exposed to the greatest concentrations of their toxic metabolites.
4. The liver is a site of drug and metabolite excretion.
5. The liver is a highly metabolic organ and is susceptible to toxicities that induce hypoxia, interactions with enzymes, or loss of energy substrates.

The potential for hepatotoxicity can be enhanced by dietary imbalance (high fat, low protein), presence of disease concurrent administration of drugs that alter hepatic drug metabolizing enzymes or hepatic blood flow (Bunch, 1993), and age (Schenkers, 1994).

Drug-induced and chemical-induced liver injury have been classified into two categories (Ockner, 1982; Plaa, 1985; Bunch, 1993). Type I toxins, or intrinsic hepatotoxins, cause Type A adverse reactions, which are predictable and dose and time dependent and occur in most, if not all, subjects exposed to appropriate doses of the substance. Any drug metabolized by the liver probably can cause some degree of type I hepatic disease simply by the production of phase I metabolites, which as a general rule tend to be toxic because of their reactivity. Type II, or idiosyncratic hepatotoxins, cause type B reactions, which are nonpredictable and dose and time independent. Their occurrence is sporadic and not reproducible.

Drug-induced hepatotoxicity (Table 3–1) is associated with a wide range of histologic changes, from acute, reversible, and clinically benign lesions to those that cause fatal massive necrosis, chronic hepatitis, or malignancy (Ockner, 1982; Plaa, 1985). Some drugs characteristically cause only a single lesion, whereas others cause multiple lesions. The lesions caused by any drug are rarely specific for that drug but can be caused by a variety of drugs or other disorders.

Table 3–1. Examples of Drugs Associated with Liver Toxicity in Small Animals*

Acetaminophen
Anabolic steroids†
Aspirin
Carprofen
Deoxycholic acid
Diazepam (cats)
Etodolac‡
Glucocorticoids
Griseofulvin (cats)
Halothane (?)
Ketoconazole
Mebendazole
Melarsomine
Methoxyflurane
Methotrexate
Mibolerone
Megestrole acetate (cats)
Oxibendazole
Phenobarbital
Phenytoin
Primidone
Sulfonamides
Thiacetarsamide

*Many other drugs that are metabolized by the liver are potentially hepatotoxic because of the production of phase I reactive metabolites.

†Particularly methylated steroids (e.g., stanozolol).

‡In the author's experience.

Frequently, drug-induced hepatic injury is limited to select regions or zones (e.g., central, middle, or peripheral) in the lobule (Ockner, 1982; Plaa, 1985). Histologic lesions associated with drug hepatotoxicity include the following (Ockner, 1982; Plaa, 1985). *Zonal necrosis* usually results from type I or predictable toxins. The production of toxic metabolites may be an important cause of zonal necrosis because drug metabolizing enzymes predominate in zones most likely to develop necrosis. In most cases of acute injury, the process is fatal or completely resolved. If exposure is chronic or recurring, however, the lesions may persist and progress, depending on the dose, agent, and health of the patient. *Lipid accumulation,* usually of triglycerides, may be associated either with little alteration of hepatic function or with both clinical and laboratory manifestations of liver dysfunction.

Nonspecific hepatitis is seldom associated with serious or progressive hepatic decompensation or failure and is fully reversible after discontinuation of the drug. *Chronic hepatitis* usually requires continued exposure and is not the result of self-perpetuation of an acute lesion. In general, prompt and complete resolution of this lesion can occur after timely discontinuation of therapy with the inciting drug. *Cirrhosis* generally requires prolonged or repeated exposure to the toxin. *Silent cirrhosis* is a term used to describe the gradual evolution of liver disease to cirrhosis without any clinical illness. Although methotrexate is among the most implicated drugs in humans, it is likely that many drugs that cause progressive liver disease do so "silently" for a long time.

Drug-induced *cholestasis* is not well understood. Drugs can target bile ducts or canaliculi, causing primarily cholestasis without hepatocellular disease. When accompanied by an inflammatory infiltrate, systemic illness usually occurs, whereas cholestasis without inflammation is associated with no or very mild clinical signs. Recovery usually occurs after discontinuation of drug therapy (Ockner, 1982; Plaa, 1985). Drugs can also affect primarily sinusoidal or endothelial cells, causing primarily *fibrosis* or *veno-occlusive disease*. Veno-occlusive disease tends to be predictable and is most commonly associated in people with anticancer drugs. An immune basis has been recognized for some drugs causing clinical signs consistent with chronic active hepatitis.

Treatment of drug-induced liver disease is primarily supportive. Because reactive metabolites are often the cause of disease, or exacerbate disease, however, use of compounds that help prevent metabolite damage to the liver should be considered. Specific examples include *N*-acetylcysteine, an intracellular form of glutathione; ascorbic acid, another type of oxygen radical scavenger; and *S*-adenosylmethionine (SAMe), a compound that contributes to a number of methylation reactions in the body (see Chapter 27).

HEPATOTOXIC DRUGS

Glucocorticoids

Glucocorticoids consistently cause diffuse to centrilobular vacuolization and perivacuolar glycogen accumulation in hepatocytes (Badylak and Van Fleet, 1981; Fittshen and Bellamy, 1984). Focal necrosis has been occasionally described in clinical cases. Similar lesions result with hyperadrenocorticism. In addition to serum biochemical changes consistent with liver disease, glucocorticoids also cause elevations in a steroid-specific alkaline phosphatase isoenzyme, which can be discerned with the levamisole test. This increase (induction) is not considered indicative of liver disease if other indicators of liver disease are absent. The pathologic changes associated with glucocorticoids are slowly reversible over 1 to 1.5 months after discontinuation of therapy.

Inhalant Anesthetics

Adverse reactions to inhalant anesthetics are unusual in veterinary medicine (Ndiritu and Weigel, 1977; Grant et al., 1984) in part because duration of anesthetic exposure is limited. Methoxyflurane administration in dogs has occasionally been associated with acute centrilobular necrosis accompanied by a mixed inflammatory infiltrate. Halothane-associated hepatic injury in the dog has not been confirmed, although a clinical report has described a single case of acute hepatic necrosis after its use. In humans, the degree and incidence of halothane-induced liver damage do not appear to correlate with the duration or number of exposures and therefore has been suggested to reflect an idiosyncratic hypersensitivity.

Anticonvulsant Therapy

Although most dogs receiving chronic anticonvulsant therapy can be expected to develop abnormalities in serum biochemistries and hepatic function tests (Bunch et al., 1984, 1987), only about 15% of dogs receiving long-term anticonvulsant therapy have been estimated to be at risk to develop serious hepatotoxicity. This risk is, however, greatly increased if drug concentrations approach the maximum therapeutic range. Primidone is probably most commonly associated with hepatotoxicity in dogs, followed by phenobarbital and then phenytoin in combination therapy. One of the many reasons that phenytoin is no longer used as an anticonvulsant in dogs is hepatotoxicity. Two distinct forms of hepatotoxicity have been ascribed to reflect the sequelae of anticonvulsant phenytoin in dogs (Bunch et al., 1987). The first (type B reaction) is characterized by clinical signs after extended treatment at lower than recommended doses and may result from an (unpredictable) idiosyncratic reaction. Indications are that histologic changes with this form will progress from chronic hepatitis to cirrhosis. The second form is more frequently characterized by intrahepatic cholestasis and is associated with a poor prognosis. This form of liver disease has been associated with high doses of phenytoin in combination with primidone or phenobarbital and may represent an intrinsic hepatotoxicity. Toxicity may be enhanced by concurrent administration of drugs (such as phenobarbital) that induce drug metabolizing enzymes and therefore increase the formation of potentially toxic (particularly phenytoin) intermediates.

In the author's experience, phenobarbital-induced hepa-

Figure 3-4. The liver from a dog that died from end-stage liver disease, presumably due to phenobarbital concentrations above 50 μg/mL for 2 months. The clinical pathology progressed from normal to indicative of end-stage disease within a 3-month period.

totoxicity (Fig. 3-4) is type A or dose-dependent, although an idiosyncratic reaction may also occur. Phenobarbital-induced hepatotoxicity is more likely to occur in patients whose phenobarbital concentrations are more than 35 μg/mL; the longer the patient is above this concentration, the more likely toxicity will occur (Dayrell-Hart et al., 1991). Although it has yet to be proved, animals requiring higher doses of phenobarbital to maintain a specific concentration of phenobarbital (even if in the therapeutic range) may be predisposed to toxicity compared with a dog that requires a lower dose to maintain the same concentration. The need for a higher dose in the former animal probably reflects enzyme induction, more rapid elimination of phenobarbital, and therefore a greater number of toxic metabolites.

Detection of phenobarbital-induced hepatotoxicity is complicated by the fact that phenobarbital also induces serum alkaline phosphatase and serum alanine transaminase activities, but the increase is not necessarily associated with hepatotoxicity. Clinical laboratory tests associated with toxicity include changes in tests indicative of hepatic damage such as increased activity of serum alkaline phosphatase, alanine transaminase, and aspartate transferase; changes in tests indicative of hepatic function, such as increased serum bile acid concentrations; and, with increasing severity, decreased serum albumin, blood urea nitrogen, and cholesterol concentrations. Toxicity can occur within several months but appears reversible if the drug is discontinued before fibrotic disease develops (Bunch, 1993).

Decreasing drug concentrations should also reduce the progression of chronic disease to cirrhotic disease, although what constitutes a "safe" target phenobarbital concentration in these patients has not been documented. Bromide therapy should be initiated for patients with liver disease (regardless of the cause) who must also receive anticonvulsant therapy (see Chapter 24). Despite its ability to cause hepatotoxicity, phenobarbital appears to be a safe and effective anticonvulsant if drug concentrations can be maintained well below the recommended maximum.

Diazepam may cause hepatotoxicity in cats (Elston et al., 1993). Reports have focused on cats receiving diazepam as an appetite stimulant rather than as an anticonvulsant. Manifestations include vomiting, depression, jaundice, lethargy, and acute death. Clinical laboratory tests associated with toxicity include increased serum alanine

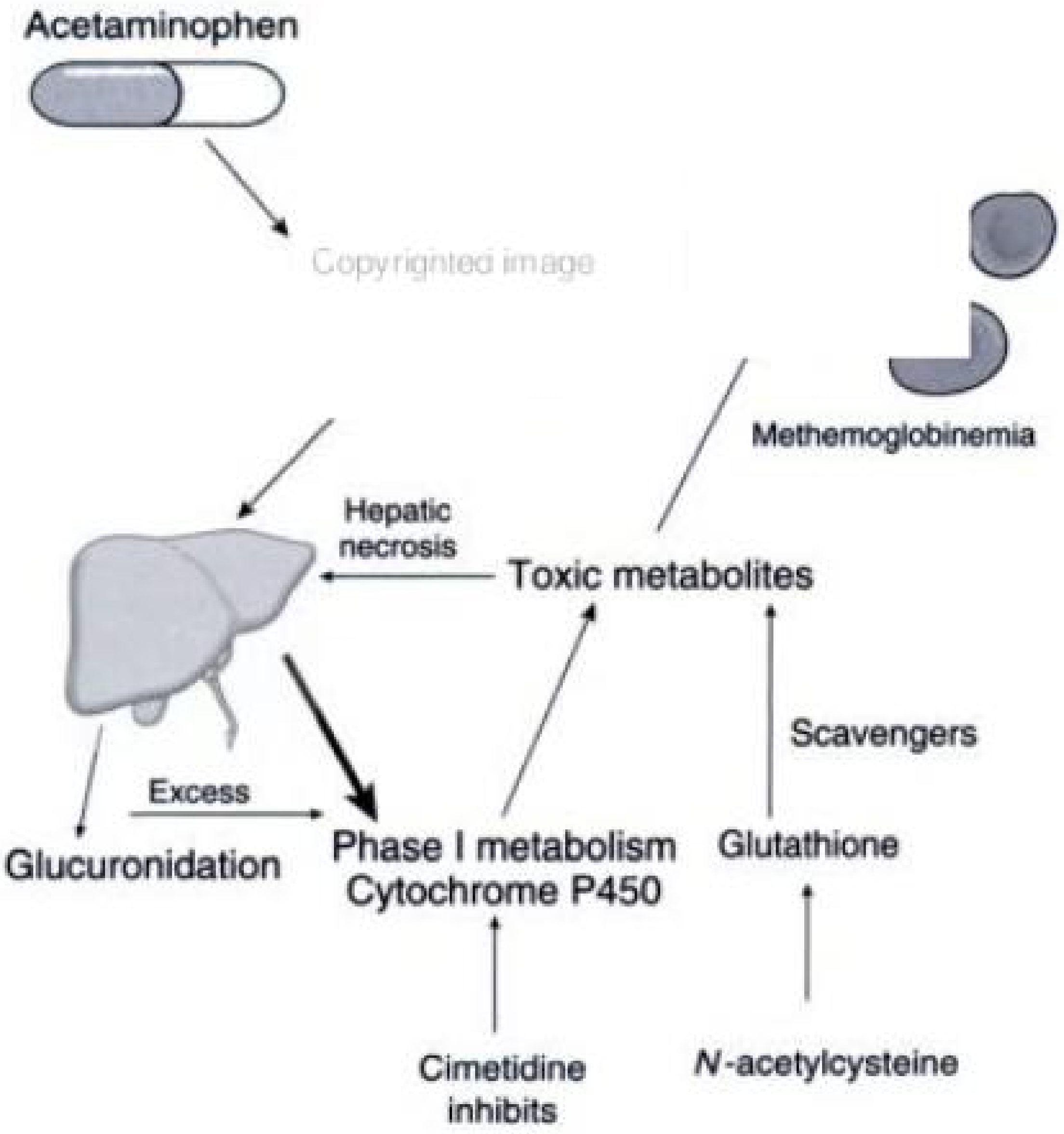

Figure 3-5. Acetaminophen toxicity reflects a cytotoxic type A adverse reaction. Because cats are deficient in glucuronidation, phase II metabolism is easily overwhelmed, and drug is shunted more aggressively back into phase I metabolism. The same process occurs in dogs after an overdose. The products of phase I metabolism are reactive and cause destruction of tissues (liver and red blood cells). Glutathione, an important phase II scavenger, prevents damage but is easily depleted in cats. Supplementation in the form of *N*-acetylcysteine can decrease damage. Cimetidine is useful because it decreases phase I metabolism and thus the formation of phase I metabolites.

transaminase, aspartate transferase, and alkaline phosphatase activities and increased bilirubin. Toxicity does not appear to be associated with the dose or duration. Toxicity has not been experimentally induced, suggesting that the reaction is idiosyncratic (i.e., nonpredictable).

Acetaminophen and Other Analgesics

Acetaminophen is a predictable hepatotoxin in the cat (Oehme, 1986), although methemoglobinemia is the predominant manifestation of toxicity. Most acetaminophen is normally conjugated to glucuronide, with a smaller portion undergoing drug metabolism to both nontoxic and toxic metabolites. Generally, the toxic metabolites are removed by glutathione conjugation. Because the cat is deficient in glucuronyl transferase, a larger proportion of acetaminophen is shunted to form toxic metabolites, which rapidly deplete glutathione (Fig. 3–5). Toxic metabolites accumulate and cause acute hepatic necrosis and systemic methemoglobinemia. Treatment is oriented toward supplementing glutathione by the administration of *N*-acetylcysteine, a gluthione precursor that can penetrate cell membranes. Cimetidine has also been suggested because it is a potent drug metabolizing enzyme inhibitor and may prevent or reduce metabolism of acetaminophen to toxic intermediates if administered within 48 hours of ingestion.

Clinical signs of aspirin toxicity (more likely in cats) are similar to those seen in human medicine (Oehme, 1986). Subtle changes in liver function reflect nonspecific hepatitis, the primary histologic lesion. Most NSAIDs are probably associated with hepatic disease, although reported incidents are isolated.

The use of carprofen has been associated with liver disease in dogs. This topic is discussed in Chapter 16.

Mebendazole and Oxibendazole

Acute centrilobular hepatic necrosis and fatal fulminating hepatitis have been reported in dogs after the clinical and experimental administration of the anthelmintics mebendazole and oxibendazole (Polzin et al., 1981; Van Cavteren et al., 1983). Clinical signs were evident in as few as 2 days or as many as 10 to 14 days after administration. Although mebendazole was originally thought to be an intrinsic hepatotoxin, other studies suggest that it is idiosyncratic.

Sulfonamides

Sulfonamides can cause toxicity of multiple organs, including the liver (Cribb, 1996; Twedt et al., 1997). There does not seem to be a difference among the sulfonamides in the likelihood of toxicity. In one report that supports an idiosyncratic reaction, the duration of therapy before hepatotoxicity developed ranged from 4 to 30 days, and the dose ranged from 18 to 53 mg/kg every 12 hours (Twedt et al., 1997).

Table 3–2. Examples of Drugs Associated with Kidney Toxicity in Small Animals

Aminoglycosides
Angiotensin-converting enzyme inhibitors
Amphotericin B
Cephaloridine
Methoxyflurane
Nonsteroidal anti-inflammatories
Sulfonamides
Thiacetarsamide
Tetracyclines

Thiacetarsamide

Thiacetarsamide (Caparsolate) is associated with hepatic injury in humans and animals. Chronic exposures in humans are more likely to cause clinically significant hepatic disease. Hepatotoxicity is, however, a common complication of acute administration of thiacetarsamide for heartworm disease in dogs, although residual effects after therapy is completed are not expected (see Chapter 30). In normal animals, melarsomine causes less hepatotoxicity and renal toxicity than thiacetarsamide (Raynaud, 1992).

Bile Acids

Bile acids are hepatotoxic, and they contribute to the development of hepatitis in patients with cholestasis, regardless of the origin. Bile acids are also used therapeutically as choleretics. Among the bile acids present endogenously and used therapeutically, however, those that are lipid soluble (i.e., deoxycholic acid) are more hepatotoxic than those that are water soluble (ursodeoxycholic acid). Ursodeoxycholic acid rather than deoxycholic acid should be used for therapy. Bile acid therapy should be discontinued in the event of cholecystectomy.

KIDNEY

Like the liver, the kidney is vulnerable to drug-induced toxicity for several reasons (Table 3–2) (Hook and Hewitt, 1985):

1. Renal blood flow accounts for 25% of cardiac output; hence the kidneys are exposed to large amounts of blood-borne drugs.
2. Reabsorption of salt and water in the proximal tubules results in progressive concentration of drugs in the glomerular filtrate.
3. Passive drug reabsorption exposes the tubules to even greater concentrations of drug.
4. The kidney contains drug metabolizing enzymes, thus increasing its exposure to potentially toxic metabolites.
5. The kidney is sensitive to extrarenal factors (e.g., those that induce ischemia or dehydration) that can predispose the kidney to or exacerbate drug-induced renal damage by drugs (Hook and Hewitt, 1985; Hornyck, 1984).

Specific cellular or subcellular sites of nephrotoxins frequently are not known. Usually a toxin affects more than one type of renal tissue because of the high drug concentrations to which the kidney is exposed. The glomerulus is susceptible to direct nephrotoxicity as well as to indirect toxicity such as that caused by immunologic injury (Hook and Hewitt, 1985). Many nephrotoxins cause predominantly proximal tubular damage. This is expected in part because blood flow is greatest in the renal cortex, where the proximal tubules are located. Variations in proximal tubular susceptibility to toxins may reflect different tubular functions (Hook and Hewitt, 1985; Engelhardt and Brown, 1987).

NEPHROTOXIC DRUGS

Aminoglycosides

Despite the nephrotoxicity associated with therapy, aminoglycosides remain an important part of antimicrobial therapy. Although the mechanism of nephrotoxicity is not completely understood, recent advances in understanding aminoglycoside actions may help prevent the incidence of nephrotoxicity (Brown et al., 1985; John, 1988; Moore et al., 1987; Powell et al., 1993; Maller et al., 1993). Aminoglycoside-induced nephrotoxicity is also discussed in Chapter 9.

Reversible renal impairment occurs in up to 25% of human patients receiving aminoglycosides for more than 3 days. Loss of prostaglandin synthesis appears to be an important part of the pathophysiology. In addition, aminoglycosides actively accumulate in the brush border of cortical proximal tubular cells and are trapped in lysosomes. During accumulation, tubular cells become damaged, and cellular enzymes and other contents are destroyed or released. Myeloid bodies containing DNA, RNA, and the aminoglycoside-filled lysosomes accumulate with eventual lysosomal disruption. Among the enzymes inhibited are phospholipases important for prostaglandin synthesis. The initial decrease in glomerular filtration that accompanies aminoglycoside therapy may be associated with the inability of the kidney to vasodilate in response to vasoconstrictor actions such as that signaled by angiotensin II.

Avoidance of aminoglycoside nephrotoxicity is handicapped by the lack of a sensitive, specific indicator of renal damage. Renal damage is first indicated by increased excretion of brush border enzymes such as alanine aminopeptidase and alkaline phosphatase, but their release is not specific for renal toxicity. Decreased renal concentrating ability, proteinuria, and cast formation are followed by a reduction in glomerular filtration rate and azotemia. These are, however, insensitive indicators because major damage has and will continue to occur by the time these abnormalities are evident. More recently, spot checks of urine creatinine to γ-glutamyltransferase activity has been suggested as a method to detect or monitor aminoglycoside nephrotoxicity (Grauer et al., 1995). Avoidance of nephrotoxicity is crucial to therapeutic success with aminoglycosides and is discussed in Chapter 9.

Nonsteroidal Anti-inflammatory Drugs

The role of prostaglandins in renal physiology is particularly important to the kidney subjected to vasoconstrictive signals. Both PGE_2 and PGI_2 cause or maintain vasodilation of renal arterioles in the face of vasoconstrictive substances. As a result, renal blood flow, glomerular filtration, and the filtered load of sodium and water are maintained, and reabsorption of sodium and water is decreased. Pathologic conditions associated with increased prostaglandin activity include decreased plasma volume such as might occur with volume depletion, cirrhosis with ascites, the nephrotic syndrome, and congestive heart failure; renal diseases (e.g., chronic renal failure, chronic glomerulonephritis, and interstitial nephritis); and selected other renal conditions such as renovascular hypertension, hydronephrosis, and ureteral obstruction.

NSAIDs inhibit the synthesis of renal prostaglandins and may lead to deterioration of renal function in patients whose kidneys are physiologically stressed (Angio, 1987; Dunn et al., 1988). Analgesic nephropathy is associated with long-term use (or abuse) of high doses of NSAIDs. The syndrome is more common in human patients than in veterinary patients, probably because therapy with NSAIDs is prolonged in the human patient and often occurs without physician supervision. NSAID therapy is also more common in geriatric patints, who are more likely to have reduced renal function. Among animals predisposed to developing analgesic nephropathy are geriatric animals; animals afflicted with conditions that impair renal blood flow (e.g., cardiac, renal, or cirrhotic liver disease); animals subjected to a hypotensive state (e.g., prolonged anesthesia without fluid support); and animals receiving nephroactive or nephrotoxic drugs in addition to the NSAID. Patients receiving more than one NSAID, aminoglycosides, or amphotericin B are potential candidates for analgesic nephropathy (Selig et al., 1990). Animals also receiving angiotensin-converting enzyme inhibitors may be more susceptible to analgesic nephropathy (Selig et al., 1990). Interstitial nephritis, a less common syndrome associated with NSAID use by human patients, has not been reported in animals. The cause of this syndrome appears to be a cell-mediated allergic response. Loss of renal prostaglandins may potentiate the disease as inflammation progresses unchecked.

Recent studies focusing on the nephrotoxic effects of NSAIDs indicate that the deleterious effects of NSAIDs on renal function may be counteracted with the PGE_1 analogue misoprostol (Fullerton et al., 1993). The cytoprotective effects of misoprostol in the gastrointestinal tract and its efficacy in the protection and treatment of gastroduodenal ulceration associated with NSAIDs have been well established. Misoprostol has been cited for its immunomodulatory, cytoprotective, and vasodilatory effects in many tissues and is being studied for its efficacy in a variety of renal conditions. It has been used clincally by human patients suffering from clinical conditions associated with peripheral or renal vasoconstriction. Controversy exists regarding the effects of misoprostol on renal function. These effects may be dose related, with natriuresis, diuresis, and vasodilation occurring at low doses and vasoconstriction and impaired salt and water excretion occurring at high doses. Misoprostol may become a drug important to the management of a variety of acute and chronic renal disorders and, in particular, drug-induced nephropathies.

Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme (ACE) inhibitors have become important in the treatment of hypertensive small animals. Among their actions, these drugs block conversion of angiotensin I to angiotensin II. Some of the pathologic sequelae that accompany stimulation of the renin-angiotensin-aldosterone (RAA) system are attenuated as angiotensin II is inhibited. The RAA system, and particularly angiotensin II, is the principal autoregulatory mechanism that maintains renal perfusion in the presence of low arterial pressures (Abbott and Bakris, 1993). In the kidney, angiotensin regulates both renal blood flow and glomerular filtration rate by modulating constriction of the postglomerular efferent arteriole. In addition, tubular sodium is reabsorbed, and renin release is inhibited. The ACE inhibitors are being actively researched for their ability to protect the kidney from progressive renal disease, including the deleterious effects of proteinuria (Gansevoort, 1997; Ibrahim 1997). However, they also are recognized as capable of causing deleterious effects on renal function.

Inhibition of ACE and thus angiotensin II results in attenuation of postglomerular efferent arteriolar constriction. As the efferent arteriole dilates, glomerular hydrostatic pressure decreases, which can lead to decreased glomerular filtration. This is particularly likely if the RAA system is activated, as may occur in volume-depleted or sodium-restricted patients. For example, patients suffering from heart failure may be predisposed to reduced glomerular filtration when ACE inhibitor therapy is begun.

As cardiac output diminishes with the progression of heart failure, reflex efferent arteriolar tone becomes increasingly important to the maintenance of glomerular filtration (Miller, 1992; Munger, 1993). As ACE inhibitor therapy is begun, inhibition of ACE results in a decrease in total peripheral vascular resistance, renal vasoconstriction, and renal perfusion pressure. Net glomerular filtration pressure decreases as renal hemodynamics change. Renal filtration generally is maintained with ACE inhibitor administration in these patients as long as cardiac output improves with therapy. Decreases in systemic vascular resistance, renal efferent arteriolar tone, and glomerular filtration must, however, be balanced by a concomitant increase in cardiac output; otherwise, glomerular filtration will decrease. Decreased glomerular filtration after ACE inhibitor therapy is more likely to occur in the presence of excessive vasodilation, moderate to severe volume depletion, or minimal myocardial reserve. Initial acute treatment of sick patients with enalapril can decrease both creatinine clearance and glomerular filtration rate. Assuming renal damage is not irreversible, however, chronic treatment generally causes glomerular filtration rate to return to baseline levels.

Amphotericin B

At least 80% of human and probably a similar percent of veterinary patients receiving amphotericin B develop renal damage and dysfunction (Hook and Hewitt, 1985; Sande and Mandell, 1986). The degree of damage is proportional to the amount and duration of therapy. Most damage is reversible once therapy is discontinued, but a small amount of residual damage usually persists. Damage occurs in both the proximal and distal tubule. Nephrotoxicity consists of intense renal arteriolar vasoconstriction, which induces ischemia and tubular damage due to binding between amphotericin and the cholesterol component of lipids of the tubular cell membranes (see Chapter 11). Changes in cell permeability result in internal cellular acidification and cell death. Clinical signs reflect renal tubular acidosis and concentrating defects (polyuria and polydypsia). Prevention of toxicity is facilitated by pretreatment with sodium-containing (isotonic) fluids, short-acting glucocorticoids and antihistamines, and concurrent administration of bicarbonate and mannitol (Pyle, 1981). Therapy with amphotericin should be discontinued if serum urea nitrogen concentrations rise above 50 mg/dL.

Other Drugs

Cephalosporins, particularly *cephaloridine,* may also cause acute proximal tubular damage (Hook and Hewitt, 1985). Cephaloridine is concentrated in the kidney, particularly in the cortex. Cephaloridine nephrotoxicity may depend on its metabolism to toxic intermediates. Although cephaloridine-induced nephrotoxicity is well recognized in humans, veterinary reports are rare (Brown et al., 1985).

The antianabolic effects of *tetracyclines* may result in elevations of serum urea nitrogens (Hook and Hewitt, 1985). In addition, tetracyclines occasionally may produce renal medullary toxicity. Outdated tetracyclines may cause proximal tubular damage characterized by polyuria, glucosuria, and aminoaciduria (a Fanconi-like syndrome).

Sulfonamides may reach large enough urinary concentrations that they crystallize and cause renal tubular obstruction. The incidence of toxicity has, however, been decreased with the advent of drug combinations in which the total amount of a single sulfonamide has been decreased. Example preparations are those containing multiple (triple) sulfonamides and the "potentiated" products containing trimethroprim in combination with a single sulfonamide. All sulfonamides should, however, still be used with caution in animals with impaired renal function, and care must be taken to maintain the hydration status of the patient (Bushby, 1980).

Methoxyflurane causes a dose-dependent, high-output nephrotoxicity in humans. Toxicity appears to be the result of oxalate metabolites and inorganic fluoride. Oxalate metabolites crystallize in and obstruct the tubules, whereas inorganic fluoride produces tubular necrosis (Polzin et al., 1981). Veterinary reports of methoxyflurane-induced nephrotoxicity are rare, probably because veterinary patients are at a reduced risk of developing nephrotoxicity because exposure (surgery) times are much shorter than in humans (Pedersoli, 1977).

Trivalent *arsenicals* such as thiacetarsamide denature proteins by binding to sulfhydryl groups. The glomerulus is often the first site of arsenical-induced nephrotoxicity, but proximal tubule damage predominates, probably because of the large number of enzymes that are denatured in this region (Hook and Hewitt, 1985). Initial proteinuria is followed by tubular necrosis and degeneration.

GASTROINTESTINAL

Most orally administered drugs are probably capable of causing nausea or vomiting simply due to irritation of the gastrointestinal tract mucosa. Erythromycin, for example, is a prokinetic agent and, as such, may cause upset in up to 50% of animals taking the drug. A patient with disease of the gastrointestinal tract is predisposed to these side effects. Many intravenous drugs also cause nausea or vomiting, particularly if given rapidly because of stimulation of the cheme receptor triggering zone. A number of drugs are recognized for their tendency to stimulate this zone regardless of the route of administration. Examples include digoxin, anticancer drugs, and most opioids.

Any drug that is antianabolic or inhibits cellular division is potentially toxic to the gastrointestinal tract by impairing the rapid turnover of epithelial cells in the mucosa (Table 3–3). Tetracyclines and chloramphenicol are antianabolic, although long-term administration is necessary before these drugs affect the gastrointestinal tract. Anticancer chemotherapeutic drugs best exemplify drugs that decrease epithelial cell turnover. Among the drugs most commonly causing gastrointestinal disease in veterinary medicine are the NSAIDs. These drugs inhibit prostaglandins, which in the gastrointestinal tract mucosa serve to inhibit gastric acid secretion, stimulate bicarbonate and mucous production and epithelialization, and increase blood flow. Among the nonsteroidal drugs most likely to cause gastrointestinal tract ulceration are aspirin—which also directly irritates the gastrointestinal tract mucosa—and ibuprofen, whose therapeutic range in the dog appears to be higher than the toxic range. Treatment of nonsteroidal induced toxicity should include sucralfate and misoprostol (prostaglandin E) and, if necessary, an inhibitor of gastric acid secretion such as ranitidine. Selected antimicrobials alter the microflora of the gastrointestinal tract and can subsequently cause diarrhea. Achlorhydria induced by a number of drugs can lead to gastrointestinal upset by changing microflora.

CENTRAL NERVOUS SYSTEM

Because of the brain's role in integrating the body, toxic injury to one of its areas can result in manifestations from another site. Likewise, drugs that cause injury to other systems can result in CNS damage due to metabolic changes (e.g., hypoglycemia, hypoxia). The high metabolic rate of neurons and the marked need for nutritional support render this system more susceptible to damage (Sipes and Dart, 1998). Neurons are uniquley dependent on the cell body to provide support for the dendrites and axons; the axon, which is devoid of metabolic function, depends on axonal transport for supplies to meet its metabolic needs. Drugs or chemicals that interfere with axonal transport (acrylamide and n-hexane) ultimately lead to axonal atrophy (Sipes and Dart, 1998). The CNS is also uniquely lacking in regenerative capacity. Lesions of CNS damage thus accumulate, leading to additive effects after subsequent exposures to a toxic compound as well as to delayed manifestations when neuronal reserve can no longer compensate for the abnormalities. Some toxicities may not occur until age-related attrition of neurons causes decompensation, thus prolonging the time between cause and effect and decreasing the likelihood of recognizing the relationship between exposure and neurotoxicity (Sipes and Dart, 1998).

Table 3–3. Examples of Drug-Induced Diseases of the Gastrointestinal System*

- Nonsteroidal anti-inflammatories (ulcerative)
- Glucocorticoids (ulcerative)
- Anticancer drugs
- Phenobarbital and phenytoin (decreased absorption of vitamins)
- Omeprazole (gastric hypertrophy)
- Many orally administered drugs (by virtue of direct contact)
  - Erythromycin
  - Digoxin
  - Fluorinated quinolones
- Altered microbial flora
  - Clindamycin

*Many drugs cause gastrointestinal upset due to direct irritation of the gastrointestinal mucosa or by stimulation of the chemoreceptor triggering zone.

The blood-brain barrier limits the incidence of adverse reactions in the CNS. Increased permeability of this barrier, however, such as might occur in pediatrics or disease, predisposes animals to CNS reactions. All CNS active drugs are likely to cause CNS "signs" if given in too high a dose. Drugs that can induce seizures in epileptic patients, and should therefore be avoided, include phenothiazines, butyrophenones, metoclopramide, tricyclic antidepressants, and reportedly (although literature is minimally supportive of this fact) glucocorticoids (Table 3–4). The CNS toxicity of ivermectin, and to a lesser degree of milbemycin, occurs due to blockade of GABA-receptor interactions (Neer, 1991; Pullium et al., 1985; Tranquili et al., 1991). The toxicity has been well documented in sensitive breeds such as collies and Australian shepherds, perhaps because of greater permeability in the blood-brain barrier. Doses as little as 100 μg/kg can cause toxicity in these breeds. Toxicity will, however, occur in any animal that is sufficiently overdosed. Clinical signs include emesis, diarrhea, salivation, fever, disorientation, ataxia, trembling, seizures, depression, coma, and blindness. Clinical signs may not occur for 2 to 3 days. Picrotoxin and physostigmine (0.06 mg/kg) slow IV have been recommended as an antidote. Picrotoxin is associated with toxicities (seizures) and its effective use is not recommended unless the patient is comatose. One report cites a dose of 1 mg/min (as a 0.1% dilution in 5% dextrose) given as an IV drip until clinical response was evident (8 minutes). Seizures in the patient responded to anticonvulsant therapy (Sivine, 1985). Supportive therapy is also indicated.

Amitraz is a monamine oxidase inhibitor that prevents the metabolism of neurotransmitters such as norepinephrine. Sedation, depression, ataxia, and weakness are the manifestations. Yohimbine, an α_2-adrenergic blocker, can be used to reverse the signs of norepinephrine accumulation. Metronidazole can cause CNS derangements in dogs receiving more than 60 mg/kg. Signs may not occur for 7 to 12 days after therapy is begun. Clinical signs include ataxia, nystagmus, and seizures. Clinical signs may take 2 weeks to resolve; therapy is supportive.

The potential for phosphate enemas to induce life-threatening CNS derangements has been well documented, particularly in cats. Toxicity is associated with hyperphosphatemia, hypocalcemia, hypernatremia, hyperglycemia, hyperosmolality, and metabolic acidosis. Onset of clinical signs (ataxia, tetany, convulsions, weak pulse, and hypo-

Table 3–4. Examples of Drug-Induced Diseases of the Central Nervous System

Drug	Manifestation
Amitraz	Sedation, ataxia, muscle weakness
Aminoglycosides	Neuromuscular blockade
Antidepressants	Hyperexcitability, depression, aggression, seizures, ataxia
Antihistamines	Sedation, excitement
Benzyl alcohol	Hypersynthesis, ataxia, aggression, depression, coma (cat)
β-lactams (cefazolin and imipenem)	Lowered seizure threshold, ataxia
Bismuth	Lethargy, somnolence
Butyrophenones	Lowered seizure threshold
Enrofloxacin	Seizures, exacerbated by coadministration of NSAIDs; dizziness
Erythromycin	Seizures, others
Glucocorticoids	Lowered seizure threshold with long-term therapy (?)
Griseofulvin	Ataxia, seizures
Hexachlorophene	Neuropathy
Ivermectin	Depression, lethargy, seizures, others
Lidocaine	Seizures
Metoclopramide	Hyperexcitability, lowered seizure threshold
Metronidazole	Ataxia, nystagmus, seizures
Milbemycin	Depression, lethargy, seizures, other
NSAID	Nonseptic meningitis (naproxen); exacerbation of seizures caused by fluorinated quinolones
Opioids	General CNS depression
Phenobarbital	Hyperexcitability, depression
Phenothiazines	Lowered seizure threshold
Quinolones	Seizures, other
Sulfonamides	Aseptic meningitis
Vincristine	Neuropathy

thermia) is rapid and may rapidly progress to death. Treatment is supportive, including calcium therapy. A similar phenomenon has been reported after administration of a phosphate-containing urinary acidifier in cats (Fulton and Fruechte, 1991). Benzyl alcohol can cause CNS toxicity, particularly in cats. The drug is rapidly metabolized to benzoic acid and subsequently to hippuric acid and benzyl glucuronide. Glucuronide deficiency in cats results in accumulation of benzoic acid after a single dose of 0.45 or 0.3 mg/kg per day. Clinical signs include hyperesthesia, ataxia, muscle fasciculations of the head and neck, aggression, salivation, depression, coma, and death.

The fluorinated quinolones have received some attention recently for their possible CNS side effects and, in particular, potentiation of seizures. The mechanism of action appears to be inhibition of GABA-receptor interactions and may (although this has not yet been proved) be facilitated by the presence of NSAIDs (Halliwell, 1991). High doses are therefore to be avoided, particularly in predisposed patients. Several other antibiotics are associated with CNS toxicity in people (Thomas, 1994). These include the β-lactams with imipenem and cefazolin being the most epileptogenic (see Table 3–4). The aminoglycosides cause peripheral neuromuscular blockade by interfering with calcium-mediated acetylcholine release. This effect is potentiated in the presence of other neuromuscular blockers and anesthetics.

Tricyclic and other antidepressants can cause a variety of CNS disorders by virtue of their stimulatory effect on several CNS neurotransmitters and potentially inhibitory effects at other sites. Because these transmitters often modulate the normal physiology of multiple body systems, the clinical manifestations of reactions to these drugs can be diverse and subtle. Manifestations related to the CNS include seizures, change in behavior, and depression. Many of the side effects caused in people probably cannot be detected in animals (e.g., blurred vision, dizziness, dry mouth). These drugs have not been well studied in animals, but clinical reports suggest up to 25% of animals may show an adverse reaction to these drugs. Clinical signs include increased or decreased appetite, hyperactivity, polydypsia, diarrhea, anxiety, and fear. The disposition of the drugs in people includes lipid solubility, hepatic metabolism, and high protein binding, all which are conducive to drug interactions. Toxicity is enhanced when drugs are used in combination. Because the effect of these drugs take several weeks to be realized, doses may be inappropriately increased, further increasing the risk of toxicity.

OTOTOXICITY

Ototoxic drugs can damage the auditory or the vestibular or both functions (Huang and Schacht, 1989; Griffin, 1988) (Table 3–5). Auditory toxicity is often unrecognized, particularly in the older patient, unless complete deafness occurs. Vestibular ototoxicity might be detected as nystagmus or head tilt. Other clinical signs (e.g., tinnitus) are likely to occur in humans, but these side effects largely go unrecognized in animals. Ototoxic drugs generally are associated with loss of hair cells in the organ of Corti, although the biochemical mechanism is seldom known. Ototoxicity can be either reversible or irreversible.

Aminoglycosides are well known for their ototoxic potential. Ototoxicity induced by aminoglycosides is irreversible. Unlike in renal tissues, aminoglycosides are not accumulated in perilymph, and drug concentrations generally are less in perilymph than in serum. The half-life of the drug is, however, much longer in the perilymph than in serum, surpassing that in serum by days to weeks. Proposed biochemical mechanisms of ototoxicity include impaired glucose metabolism or inhibition of polyphosphoinositide turnover. Ototoxicity is enhanced by the presence of loop-acting diuretics such as furosemide. Although allowing serum drug concentrations to become nondetectable does not necessarily prevent ototoxicity, low trough concentrations are still the best means of preventing ototoxicity. The potential for ototoxicity varies among the aminoglycosides,

Table 3–5. Examples of Drugs Associated with Ototoxicity

Aminoglycosides (enhanced by furosemide)
Aspirin (not other NSAIDs)
Chlorhexidine
Cisplatin
Furosemide
Iodophors
Local anesthetics (lidocaine, bupivacaine)
Propylene glycol
Quaternary ammonium disinfectants
Tricyclic and other antidepressants
Vinblastine
Vincristine

with streptomycin surpassing that of the other aminoglycosides. There is, however, no consistent pattern in the potential for ototoxicity caused by gentamicin, tobramycin, or amikacin. Netilmicin, the newest of the aminoglycosides, may cause the least ototoxicity. Fluorinated quinolones also may cause ototoxicity when given topically.

Other drugs that cause irreversible ototoxicity include vincristine and vinblastine. Cisplatin is a newer antineoplastic drug that causes irreversible ototoxicity after accumulation of multiple doses. Toxicity occurs in the hair cells of the organ of Corti and causes predominantly auditory damage. Toxicity can be unilateral (hence may not be recognized) or bilateral. Occasionally ototoxic effects are transient.

Some disinfectants (e.g., 0.5% chlorhexidine in 70% alcohol) or carrier agents (e.g., propylene glycol) can cause ototoxicity. These drugs cause both vestibular and auditory side effects. Whereas chlorhexidine can cause almost complete destruction of the vestibular and auditory apparatus (in animal models), 70% alcohol does not appear to cause any ototoxicity. Quarternary ammonium disinfectants (e.g., 0.1% benzethonium or benzalkonium chloride) are among the most ototoxic compounds studied. Iodophors also cause ototoxicity, but damage will not be as profound as with quarternary ammonium compounds.

Several drugs cause reversible ototoxicity. Most notable are the loop diuretics such as furosemide. The ability of furosemide to enhance aminoglycoside ototoxicity when the two are given in the same patient has been well documented. Furosemide can also, however, cause ototoxity when given by itself, particularly at high intravenous doses. Hearing loss induced by furosemide may be transient. Damage appears to occur in the cochlea.

Aspirin, but apparently no other NSAID, can cause transient hearing loss. Clinical signs generally resolve within 48 to 72 hours. Several possible sites of damage have been recognized, including a vascular basis (i.e., loss of vasoactive prostaglandins) or impaired neurotransmission. Other drugs known to cause ototoxicity include local anesthetics (0.5% lidocaine can cause cochlear damage), tricyclic antidepressants, and, very rarely, β-blockers.

INTEGUMENT

The skin is the organ that most commonly manifests drug reactions in people (Wokenstein and Revus, 1995). Although the reactions are generally mild, they can become life threatening. The type of lesion varies and includes almost any type of lesion described in the skin. Lesions include wheal and flare reactions, erythema, blisters, lichenoid lesions, purpura, changes in pigmentation, necrosis, pustular lesions, and changes in hair growth. As in many organs, because the skin contains drug metabolizing enzymes, reactions can be due to either or both the parent compound or its metabolites. The most common reactions are erythematous macular or papular rashes that resolve in several days even if untreated. These manifestations may also, however, be a prelude to a severe manifestation and thus should be followed closely.

Drug-induced skin reactions may be a manifestation of an allergic response or an autoimmune disease mediated by the skin. Both type A and type B reactions occur in the skin. Of the type B reactions, all types of allergic reactions (i.e., types I through IV) can involve the skin. Type IV reactions are best exemplified by contact dermatitis. "Late" reactions include allergic vasculitis, purpura pigmentosa, and erythema multiforme. A distinct form of allergic reactions has been reported in humans and animals, involving the interaction of a drug (or its metabolite) with ultraviolet radiation; the lesion often manifests in light-exposed skin. Fixed drug eruptions are not well understood. In humans, they are characterized by erythema, often with a central blister, and may occur because regulation of adhesion molecules in the epithelium is disrupted. Drugs are capable of causing autoimmune reactions in the skin, including lupus erythematosus, pemphigus, and pemphigoid skin lesions. Life-threatening drug-induced reactions that occur in the skin of people include the Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), hypersensitivity syndrome, serum sickness, vasculitis, and angioedema.

Lesions of SJS and TEN may be hard to differentiate; SJS may be a milder form of TEN. Both appear as "scalded skin" and reflect a cell-mediated cytotoxic reaction against keratinocytes (Fig. 3–6). The diseases are characterized by blistering and extensive detachment of the epidermis. The lesions are irregular in shape and are distinguished from erythema multiforme, another drug reaction of the skin, by the irregular shapes and absence of a well-defined border and edematous ring. Both TEN and SJS tend to affect the trunk, whereas erythema multiforme has an affinity for extremities. Mucous membranes are frequently involved, and patients are generally febrile, particularly with TEN. The presence of neutropenia is interpreted as a poor prognosis in human patients suffering from TEN. Treatment of TEN includes a management protocol similar to that for extensive burns; infection with *Staphylococcus aureus* (which by itself can cause a "scalded skin" lesion) is likely to complicate therapy. Drug reactions are the primary causes of SJS and TEN; erythema multiforme is caused by selected microorganisms as well as by drugs. Drugs associated with TEN and SJS in humans include sulfonamides, anticonvulsants, allopurinol, oxicams, and (less frequently) other NSAIDs.

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Figure 3–6. Toxic epidermal necrolysis in a Doberman treated with chloramphenicol. Although the lesion is several weeks old, damage was evident within several days of intramuscular treatment.

The term *hypersensitivity syndrome* has been used in the past to refer to any skin adverse drug reaction. As such, however, it encompasses a wide variety of skin lesions, each treated differently. More recently, the term has been used in human medicine for a syndrome characterized by mucocutaneous eruptions, fever, lymphadenopathy, hepatitis, and eosinophilia. Arthritis or nephritis may also develop. As with SJS and TEN, sulfonamides and anticonvulsants are the most common causes of drug hypersensitivity.

Vasculitis occurs as a result of necrosis and inflammation in blood vessel walls, most commonly in the lower extremities, after antibody interaction with blood vessel walls. Drugs are the primary cause of vasculitis in people. Penicillins, sulfonamides, thiazide diuretics, phenytoin, and propylthiouracil are the most common interaction-related drugs. Serum sickness-like lesions in the skin also can appear as vasculitis. Lesions result from immune complex deposition in small vessels followed by complement activation and white blood cell infiltration. Lesions appear first as erythema and then progress to more severe eruption. Patients are usually febrile. Drugs that cause serum sickness manifested as dermatologic lesions in people include selected cephalosporins, minocycline, penicillins, and propranolol.

Dermatologic manifestations of type I hypersensitivities occur at mucocutaneous junctions (including the mucous membranes of the eyes, mouth, nose, lips, or tongue) or present as pruritus, flushing, erythema, and urticaria. Of these, angioedema is the most life threatening because of the risk of upper airway obstruction. Treatment includes epinephrine (for acute respiratory distress), antihistamines, and glucocorticoids.

Skin eruptions have been attributed to a number of drugs in small animals (Table 3–6). Type I skin lesions accompany many cancer chemotherapeutic agents and gold-containing antiarthritic agents. Prednisone and phenytoin can cause alopecia. Most skin reactions reflect type B adverse drug reactions, however, and as such are largely nonpredictable. Alopecia has been reported after oral administration of hetacillin (cat), prednisone (dog), parenteral gold therapy (dog), and phenytoin (dog and cat). Eczematous dermatitis has resulted from oral administration of sulfa drugs (dogs and cats), griseofulvin, diethylcarbamazine, and fluorocytosine. Topical neomycin-triamcinolone preparations and coal tar shampoos can produce generalized eczematous reactions. Generalized exfoliation has resulted from oral administration of quinidine, topical administration of lime sulfur dips, and the use of flea collars. Fixed drug eruptions have resulted from the oral administration of ampicillin and the intravenous administration of sodium thiacetarsamide. Pemphigus vulgaris-like reactions have followed thiabendazole oral therapy, and similar lesions have been reported with gold therapy. Erythematous dermatitis has been reported after the parenteral administration of a phenothiazine derivative. Pruritus has been reported after oral diethylcarbamazine, gold, and bromide (anticonvulsant) therapy. Purpura and lesions typical of TEN have occurred after oral administration of chloramphenicol (Fig. 3–6). Intravenous vitamin K and oral tetracyclines have caused urticaria and angioedema in the dog. Drug eruptions have also been associated with the systemic administration of levamisole. Human recombinant products such as erythropoietin have caused skin or mucocutaneous lesions typical of allergic drug reactions in dogs.

Table 3–6. Examples of Drugs Associated with Dermatologic Manifestations of Adversity

Drug	Lesion
Ampicillin	Fixed drug eruption
Anticancer drugs	Alopecia
Bromide	Pruritus
Coal tar shampoos	Generalized eczema
Chloramphenicol	Purpura, TEN
Diethylcarbamazine	Eczematous dermatitis, pruritus
Erythropoietin, human recombinant	Skin or mucocutaneous lesions
Flea collars	Generalized exfoliation
5-Fluorocytosine	Eczematous dermatitis
Glucocorticoids	Alopecia, hyperpigmentation
Gold-containing drugs	Alopecia (dog), pruritus, pemphigus vulgaris-like reaction
Griseofulvin	Eczematous dermatitis
Hetacillin	Alopecia (cat)
Levamisole	Drug eruptions
Lime sulfur dips	Generalized exfoliation
Neomycin (topical)	Generalized eczema
Phenothiazine derivatives	Erythematous dermatitis
Phenytoin	Alopecia
Prednisone	Alopecia (dog)
Quinidine	Generalized exfoliation
Sulfonamides	Eczematous dermatitis
Tetracyclines (oral)	Urticaria, angioedema
Thiabendazole	Pemphigus vulgaris-like reaction
Thiacetarsamide	Fixed drug eruption
Vitamin K (intravenous)	Urticaria, angioedema

Hormonal therapy is often associated with predictable skin lesions, including bilaterally symmetric alopecia and hyperpigmentation (see following discussion of the endocrine system). The effects of glucocorticoids on the skin have been well documented and are often manifested as part of the cushingoid presentation of animals receiving therapy.

Several in vivo and in vitro diagnostic tests have been developed for the detection of drug-induced adverse skin reactions in people. In general, tests studied in dogs and cats have not proved effective and, if effective, are not yet practical.

ENDOCRINE SYSTEM

Mechanisms of drug interference with the thyroid and adrenal axes have been documented in human patients (Table 3–7). Each axis presents several targets for drug interference. Mechanisms that decrease hormone concentrations include suppression of hormone release at each level (i.e., hypothalamus, pituitary, or target organ), often because hormone synthesis is decreased, or altered peripheral metabolism of the hormone (e.g., thyroid hormones) (Boothe, 1995). The latter effect is often the result of induction of hepatic drug metabolizing enzymes. Potent inducers of hepatic drug metabolizing enzymes include phenobarbital, phenytoin, and rifampin. Whether or not patients show clinical manifestations of hormone deficiency after induction of metabolizing enzymes remains to be documented. Less commonly, hormone concentrations are

Table 3–7. Drug-Induced Physiologic Changes in the Adrenocortical and Thyroid Axes*

Drug	Comment
Cortisol	
INCREASED	
Anticonvulsants	
Corticotropin	Diagnostic intent
Cortisone	For at least 24 hours
Estrogen	Increases binding globulin concentrations
Ethanol	High IV doses
Fluocinolone	After topical administration
Hydrocortisone	For at least 24 hours
Insulin	Marked effect with insulin-induced hypoglycemia
Lithium	
Metoclopramide	After IV dosing
Opiates	Within 1 hour of IV dosing with selected drugs
OPPPD (mitotane)†	Therapeutic intent
Prostaglandin F_2	Slight effect
Vasopressin	Mild increase
DECREASED	
Barbiturates	Preoperative use
Beclomethasone	After inhalant administration
Clonidine	In growth hormone-deficient children
Danazol	Displacement from binding and increased free drug
Deoxycorticosterone	After topical administration
Dexamethasone†	Diagnostic intent
Ephedrine	Accelerated clearance due to increased hepatic blood flow and enzyme activity
Etomidate	Direct suppression of adrenal function
Fluocinolone	After topical administration
Thyroxine	
INCREASED	
Dessicated thyroid	
Estrogens	Increased binding capacity of globulin for up to 1 month
Fluorouracil	Increased binding capacity
Glucocorticoids	Inhibition of conversion
Halothane	Increased release from liver
Insulin	Increased release from liver
Levothyroxine	Suppression of endogenous hormone; exogenous measured
Lithium	Report in one patient suffering from presumed drug-induced thyrotoxicosis
Phenytoin	
Propranolol	Blockage of iodothyronine deiodination in hyperthyroid and euthyroid patients
Prostaglandins	Direct effect
Tamoxifen	
Thyroid	
Thyrotropin	
TRH	
DECREASED	
Aminosalicylic acid	Prolonged administration may cause hypothyroidism
Anabolic steroids	Decreased binding to globulins
Androgens	Decreased binding to globulins up to 1 month past administration
Anticonvulsants	
Asparaginase	
Aspirin	Displaces T_4 from binding sites to prealbumin
Barbiturates	Competition for binding to prealbumin
Bromocriptine	In hypothyroidism (response to TRH unchanged)
Carbamazepine	Induction of hepatic enzymes; increased extrathyroidal metabolism
Thyroxine *Continued*	
DECREASED *Continued*	
Chlorpromazine	Increased metabolism by liver
Cholestyramine	Decreased intestinal absorption
Glucocorticoids	Up to 1 week after therapy
Diazepam	Competition for transport proteins
Furosemide	Displacement from binding sites and enhanced clearance
Growth hormone	Inhibition of TSH response to TRH(?)
Heparin	Modified binding to transport proteins(?)
Iodides†	Decreased synthesis (therapeutic)
Lithium	Reduced thyroidal iodine uptake, iodination of tyrosine, release of T_4; hepatic metabolism of T_4 to T_3
Methimazole†	Therapeutic intent
Mitotane	Competes with T_4 for binding globulin
Penicillin	Competes for binding globulin
Phenobarbital	Induction of hepatic enzymes
Phenylbutazone	Impaired synthesis, competition for binding to albumin
Phenytoin	Displacement from binding proteins; induction of hepatic enzymes
Potassium iodide	
Propylthiouracil†	Inhibits synthesis (iodination of tyrosine); therapeutic intent
Ranitidine	Slight reduction
Salicylate	Competition for transport proteins
Somatostatin	Inhibition of TSH release(?)
Stanozolol	
Sulfonamides†	
Terbutaline	Mild decrease
Triiodothyronine	
Triiodothyronine (Thyronine)	
INCREASED	
Estrogens	Increased binding capacity to transport proteins
Fluorouracil	Increased binding capacity to transport proteins
Heparin	Interference with binding to protein
Insulin	45 minutes after injection; release from liver
Phenytoin	
Prostaglandins	
Tamoxifen	
Terbutaline	
TRH	Percent free T_3 unchanged
L-Thyroxine	
Triiodothyronine	
DECREASED	
Androgens	Decreased binding capacity (diminution of transport proteins)
Anticonvulsants	
Asparaginase	
Aspirin	
Carbamazepine	Increased extrathyroidal metabolism
Cimetidine	Reduced response to TRH
Furosemide	
Glucocorticoids	Inhibition of conversion
Iodides	Inhibition of conversion
Lithium	See under Thyroxine
Phenytoin	See under Thyroxine
Potassium iodide	
Propranolol	Membrane stabilization (see under Thyroxine)
Propylthiouracil	
Salicylate	See under Thyroxine
Somatostatin	See under Thyroxine
Stanozolol	See under Thyroxine
Sulfonamides†	

Abbreviations: IV = intravenous.

*Table reflects serum or plasma values only and is based on information reported by Young (1990).

†Reported in the veterinary literature.

physiologically increased by drugs. Again, changes in hepatic metabolism are a common cause. Potent inhibitors of hepatic drug metabolism include cimetidine, chloramphenicol, and ketoconazole.

Drugs can also increase hormone concentrations by competing with and displacing the hormone from carrying proteins. The protein from which hormones are most likely to be displaced is albumin, a nonspecific carrier of many weakly acidic drugs (e.g., NSAIDs). Competition for albumin-binding sites may be less important for those hormones carried by specific carrier proteins, although competition for binding sites has been documented even for these binding sites. In some cases, a drug may influence blood hormone concentrations simultaneously at several physiologic sites, complicating interpretation (e.g., the effects of phenytoin on thyroid hormone concentrations). Because animals differ physiologically, extrapolation between species regarding the effect of a drug must be done cautiously. Caution is also advised when extrapolating results of studies in normal animals to the animal suffering from a disease of the endocrine system. For example, propranolol decreases thyroid hormone concentrations in hyperthyroid humans but not in euthyroid dogs (Center et al., 1984).

In some instances, the drug effect on a hormone is well known and is used either diagnostically (e.g., dexamethasone-induced decrease in cortisone or xylazine-induced growth hormone secretion) (Kemppainen, 1984) or therapeutically (propranolol or propylthiouracil-induced inhibition of thyroxine [T_4]). More commonly, the effect is undesirable. Several examples of undesired, drug-induced physiologic changes in endocrine function have been documented in small animal patients. The example most documented in small animals are the effects of drugs, and particularly glucocorticoids, on the hypothalamic-pituitary-adrenal axis. Interference with this axis can become clinically detrimental. Suppression of the adrenal axis by glucocorticoids is most marked after administration of depo (repositol) forms (e.g., those containing acetate esters) (Spencer et al., 1980). Interference has also, however, been documented after administration of a single dose of prednisolone or triamcinolone; multiple doses of methylprednisolone (Spencer et al., 1980); topical administration of triamcinolone (Roberts et al., 1984); and ophthalmic administration of prednisone (Zenoble and Kemppainen, 1987).

Glucocorticoids are not the only drugs that interfere with the hypothalamic-adrenal axis. The imidazole antifungal drug ketoconazole inhibits the cytochrome P450 enzymes responsible for the synthesis of both sex and adrenal steroids (Hostettler et al., 1988). Suppression of testosterone and cortisol has been documented in dogs after oral administration of 10 mg/kg once daily (Willard et al., 1986). Hormone concentrations are lowered by day 1 and remain low at day 5. Progesterone concentrations increase as testosterone concentrations decrease. The magnitude of testosterone inhibition by ketoconazole apparently resolves, with testosterone concentrations being less predictable 1 month after therapy was started. The inhibitory effect of ketoconazole on testosterone and adrenal steroids has been used therapeutically in the treatment of prostatic cancer and benign prostatic hypertrophy, and hyperadrenocorticism respectively. The newer imidazole antifungal drugs do not appear to inhibit steroid synthesis as effectively as ketoconazole.

Drug interference with evaluation of the thyroid axis is also important because of the prevalence of thyroid dysfunction in small animals. Several drugs, targeting various sites, interfere with thyroid function testing (see Table 3–7) (Wenzel, 1981). Thyroid-stimulating hormone (TSH) response to thyroid-releasing hormone (TRH) is altered by a number of drugs that modulate neurotransmitter (e.g., serotonin, dopamine) concentrations in the brain. Glucocorticoid suppression of TSH response to TRH has been well documented. Higher doses appear to suppress hypophyseal inhibition of TSH, whereas low doses interfere with the hypothalamic response (Wenzel, 1981). Note, however, that interference of the thyroid axis by glucocorticoids does not preclude simultaneous testing of the thyroid and adrenal axes in healthy dogs (Moriello et al., 1987; Reimers et al., 1982). Antithyroid drugs such as propylthiouracil and methimazole are used therapeutically to block thyroid hormone synthesis.

The effects of iodide- and iodine-containing products (including radiographic contrast agents) on thyroid hormone concentrations are well recognized and used therapeutically. Through hypothalamic regulation, iodines cause a rapid increase in TSH response to TRH as T_4 and triiodothyronine (T_3) concentrations decrease. Potentiated sulfonamides can have a profound effect on thyroid function (Campbell et al., 1995). Decreased concentrations in peripheral hormones are associated with follicular cell hypertrophy and hyperplasia and with decreased colloid formation. Changes are profound as early as 21 days yet resolve within 3 weeks after therapy is discontinued. These effects occur at high doses that might be used for difficult-to-treat, yet presumably susceptible higher bacterial or protozoal infections (>60 mg/kg per day but may also occur at lower doses).

The effects of anticonvulsant drugs, especially phenobarbital and phenytoin, on thyroid hormone disposition are less appreciated. Several sites of interference have been identified for anticonvulsant drugs. Displacement of T_4 by highly protein-bound drugs (e.g., phenytoin) from T_4-binding globulin increases T_4 concentrations; induction of hepatic drug metabolizing enzymes results in increased clearance of both T_4 and T_3; and increased conversion of T_4 to T_3 by peripheral tissues further decreases T_4. The latter mechanism has been postulated as the reason that T_3 concentrations remain normal despite increased T_3 clearance (Senuty et al., 1988) in patients receiving phenytoin.

Clinical signs of hypothyroidism may not be apparent in such cases. Note, however, that both serum T_4 and free T_4 may be decreased in some patients receiving anticonvulsants. Anticonvulsants (phenytoin) may also have a direct negative effect on TSH response to TRH. Drug-induced changes in T_4-binding globulins have also been documented in human patients taking anticonvulsants. Thyroxine and TSH concentrations should be used to diagnose hypothyroidism in animals receiving anticonvulsants (Senuty et al., 1988). Note that thyroid supplementation suppresses response to TSH, and testing should not be performed until supplementation has been discontinued for 4 to 6 weeks.

HEMATOLOGIC DYSCRASIAS

As with any drug-induced disorder, the lack of universally standardized definitions of what constitutes an adverse re-

Table 3–8. Examples of Drugs Associated with Hematologic Disturbances

Drug	Manifestation
Acetaminophen	Methemoglobinemia (especially in cats)
Anticancer drugs	Bone marrow suppression*
Azodye (urinary antiseptics)	Methemoglobinemia (cats)
Benzocaine (and related drugs)	Methemoglobinemia (cats)
Chloramphenicol	Bone marrow suppression
Cimetidine	Thrombocytopenia
Coumarin derivatives	Coagulation dysfunction
Erythropoietin (human recombinant)	Anemia
Estrogens	Bone marrow suppression
Griseofulvin	Bone marrow suppression
Heparin	Thrombocytopenia, platelet dysfunction, coagulation dysfunction
Methimazole	Methemoglobinemia
Methylene blue	Methemoglobinemia (cats)
NSAIDs	Platelet dysfunction
Phenobarbital	Neutropenia
Phenylbutazone	Bone marrow suppression
Propylthiouracil	Methemoglobinemia
Ranitidine	Anemia

*Bone marrow suppression might be manifested as anemia, leukopenia, thrombocytopenia, or any combination thereof.

action complicates recognition of hematologic disorders induced by drugs. The criteria for drug-induced hematologic disorders have been described for humans and are based on cell count, assessment of time to onset after drug exposure and time to resolution of signs after the drug has been discontinued, and the course of the reaction (Benichou and Celigny, 1991). Drug-induced hematologic dyscrasias may reflect a bone marrow response or an effect on peripheral tissues, including blood components (Table 3–8). Bone marrow suppression can result in pancytopenia or affect only a single cell line (i.e., anemia, leukopenia, or thrombocytopenia) (Stroncek, 1993). Both direct bone marrow suppression and toxicity to mature circulating cells may occur.

Bone marrow and peripheral cells are susceptible to both drugs and their metabolites; reactions may have an immunologic or nonimmunologic basis. Although drug allergies are a well-recognized cause of damage to stem cells of the bone marrow, many drugs are directly toxic. Discerning an immunologic basis can be difficult, however, if the antibodies involved have not been identified. Drugs most commonly associated with nonimmune-mediated bone marrow suppression include most cancer chemotherapeutic agents because of their predictable effects on DNA and cell division. Other drugs associated with nonimmune-mediated bone marrow dyscrasias include phenylbutazone, estrogen derivatives, and chloramphenicol. Phenobarbital has caused leukopenia and other hematologic disorders when used to treat epilepsy; white cell counts normalize once the drug is discontinued.

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Figure 3–7. Facial edema in a cat with acetaminophen toxicosis. The mucous membranes of this cat were cyanotic.

Drugs that affect blood components and the manifestations of anemia include all NSAIDs, but particularly aspirin (reflecting inhibition of platelet activity), anticoagulants such as warfarin derivatives, and heparin (these generally reflect a relative overdose). Red blood cell malfunction may occur as a result of methemoglobinemia in cats. Several reasons have been suggested for an apparent increased sensitivity of cat red blood cells to methemoglobin formation: Feline hemoglobin may be more sensitive to oxidation; feline erythrocytes may contain lower concentrations of intracellular glutathione; the proportion of subtypes of hemoglobin may differ; and, finally, feline hemoglobin may contain more sulfhydryl groups, which are reactive, than other species. Drugs associated with methemoglobinemia in cats include urinary antiseptics containing methylene blue or azodyes, acetaminophen (Fig. 3–7) and related compounds, benzocaine, DL-methionine, propylthiouracil, and methimazole.

Human recombinant erythropoietin and granulopoietin have been used to treat anemias associated with chronic renal disease and leukopenia induced by disease (i.e., parvovirus) or drugs (i.e., anticancer drugs) in dogs and cats. Unfortunately, these proteins are foreign, and antibodies may develop after 10 to 14 days, destroying not only the exogenous drug but also endogenous factors.

PULMONARY TOXICITY

Although occasionally compounds toxic to the lungs arrive by hematogenous routes, most pulmonary toxicities result from direct exposure of the respiratory tract through the nasopharyngeal or oropharyngeal airways and subsequently the tracheobronchial tract and alveoli (Sipes and Dart, 1998). Gaseous and particulate toxicants are most common. The airways may also serve as a means of systemic exposure if the toxicant is effectively and rapidly absorbed by the respiratory mucosa. Particulate matter that is impacted on the airways (generally 5 to 10 μm in size for the tracheobronchial tree and less than 5 μm in size for alveoli) can become trapped in the airways.

The mucociliary apparatus may remove entrapped particulate matter before a toxic response occurs. Some chemicals, however, cause direct injury to upper airways (chlorine, ammonia, water-soluble gases, and chromium). Compounds depositing in the alveoli can be removed only by blood flow (if the compound is absorbed), biotransformation by Clara cells or type II alveolar cells (which contain cytochrome P450 enzymes), or macrophages.

Pulmonary edema, manifested as an acute respiratory distress syndrome, is caused by severe exposure of the alveoli (in people) to acute toxicants such as phosgene, chlorine, xylene, and nitrogen oxides. Because the lung is the shock organ in cats, type I allergic reactions may manifest as primarily acute respiratory difficulties. Biotransformation in the lung, as in other tissues, may be a source of a toxic compound as an innocuous chemical is converted into a toxic one (e.g., paraquat, a herbicide metabolized by type II alveolar cells). Macrophage clearance may reflect phagocytosis; macrophage death is accompanied by the release of inflammatory mediators that can damage surrounding cells and contribute to the toxic effects of a drug. Compounds that cause pulmonary injury in humans due to the inflammatory response include asbestos, beryllium, coal dust, silica, and tungsten (Sipes and Dart, 1998).

MISCELLANEOUS DISORDERS

Potentiated sulfonamides have been associated with a variety of apparently immune-mediated disorders (Cribb, 1996). Pharmacologic toxicities include blood dyscrasias associated with folate deficiency due to inhibition of dihydrofolate reductase (thrombocytopenia and neutropenia); renal tubular acidosis; nausea and vomiting; headache and neurologic disturbances (humans); hypoglycemia; and hypothyroidism (due to inhibition of thyroid peroxidase). Intrinsic toxicities include renal toxicity associated with crystalluria, tubular necrosis or granulomatous interstitial nephritis, methemoglobinemia, and keratoconjunctivitis sicca. Keratoconjunctivitis sicca appears to be related to duration of exposure, but it may also be idiosyncratic. Alternatively, sulfonamides may cause direct toxicity to the lacrimal gland. Idiosyncratic toxicities include drug fever, dermatopathies, liver disease, pneumonitis, meningitis, myocarditis, polyarthritis (due to serum sickness), interstitial nephritis, blood dyscrasia, hemolytic anemia, uveitis, and hypothyroidism. In dogs, the most common syndrome appears to be sterile polyarthritis. Reports have been more common, although not limited to, Dobermans.

The ability of fluorinated quinolone antibiotics to cause acute retinal damage is now being examined.

AVOIDING TOXIC REACTIONS

Recommendations for avoiding specific toxicities have been given or are described in specific chapters for some of the described drugs. Appendix 5 offers antidotes for many drugs. In general, the incidence of type A adverse (predictable) reactions may be reduced by

1. Obtaining a definitive diagnosis before treatment
2. Using proper drugs according to recommended protocols
3. Using alternate (less toxic) drugs when available
4. Thoroughly evaluating the patient before and during treatment (e.g., physical examination and clinical pathology) with an emphasis on target organs of toxicity
5. Evaluating the responses to therapy and discontinuation of therapy if therapeutic effects are not evident
6. Frequent patient monitoring for remission of clinical signs and discontinuing therapy as early as possible
7. Altering dosage regimens of drugs that are likely to be accumulated to plasma levels associated with adverse reactions
8. Minimizing multiple drug therapy and minimizing use of drugs known to cause drug interactions
9. Alternating administration times for patients receiving multiple drug therapy, thus reducing the potential for drug interactions

Client education as to the potential toxicity of a drug and the clinical signs associated with its use are also important.

Type B reactions are difficult to avoid because they are unpredictable. An awareness of potential toxicities will facilitate their avoidance. Frequent patient monitoring during therapy is the best means of reducing type B adverse reactions.

REPORTING ADVERSE DRUG REACTIONS

Identifying an adverse drug reaction can be very difficult. In human medicine, methods have been defined through which the causal relationship between a suspected reaction and a suspected drug can be assessed. None are universally accepted, but each includes some or all of the following criteria: the time between the administration of the drug and the onset of the reaction or the cessation of the drug and resolution of clinical signs; the course of the reaction, which may vary if the drug is continued or interrupted; the role of the drug and underlying disease being treated as a cause of the reaction; response to re-administration of the drug; results of laboratory tests; and the history of previous administration of the drug (Benichou and Celigny, 1991).

Identifying an adverse drug reaction and communicating this information to the veterinary profession is difficult, especially for human drugs not approved for use in animals. Although safety studies are a required step in the Food and Drug Administration's (FDA's) approval of all human drugs, the focus of the animal studies is human safety. Information regarding the safety of drugs often is considered proprietary information and may not be available even on request. In addition, studies in both humans and animals intended to detect toxicity are usually performed in healthy patients, and the sample size is very small in relation to the population that will use the drug.

Thus, often an adverse drug reaction to approved drugs may not be detected until a drug is in widespread use (i.e., after the drug is available for marketing). Even then, an adverse drug reaction migth be lost to report. For example, a drug that causes side effects in 1 of 3000 patients (which might be considered a high incidence) must first be used in 3000 patients before one case occurs. The reaction might be missed if the patient is ill, because clinical signs due to the reaction will be complicated by those associated with the disease being treated. More than one drug might be used, and discerning which drug is responsible for a reaction might be difficult. Even if a reaction is detected, it must be reported so that the association between the drug and the side effect can become known among members of the profession.

Several avenues are available for reporting an adverse drug reaction (Appendix 7). First, the pharmaceutical company can be directly informed by calling the Medical Affairs officer. Second, the FDA, and for animals, the Center for Veterinary Medicine in particular, has an adverse drug reaction report protocol. Finally, the United States Pharmacopeia (USP) also has an adverse drug reaction report protocol. Their protocol is unique in that it is a "one shot" report because the USP will, in turn, notify both the manufacturer of the product and the FDA of the reaction. For both human and veterinary drugs, these resources might also be considered a source of previously reported drug reactions. Note that the USP and FDA do not attempt to judge the likelihood that a suspected reaction was, in fact, caused by the drug. In its reporting process, however, the FDA "grades" the reaction in a manner that does discriminate to some degree between likely and unlikely reactions, but confirmation rarely is available. Addresses and information, including forms, regarding these databases, are given in Appendix 7.

CLINICAL LABORATORY TESTS

A drug-induced disease is often first suspected based on an abnormality in a diagnostic test that cannot be easily attributed to a disease process. Many drugs cause changes in diagnostic tests but are not associated with disease. Confirming the cause and effect relationship between drug and abnormalities can be very difficult unless the drug can be discontinued and then re-administered.

Drugs interfere with diagnostic tests either directly at the level of the analytical procedure (in vitro) or by induction of a physiologic change in the patient (in vivo) (see Table 3–7). Of the two levels of interference, it is likely that analytical interferences will occur regardless of the species from which the sample was collected. Thus, interferences affecting analytical procedures are better documented in veterinary medicine because they generally can be extrapolated from human analytical testing. Mechanisms of in vitro interference vary. Drugs that interfere with endocrine testing are described as adverse drug reactions of the endocrine system.

If analytical (in vitro) interference by a drug is suspected, the laboratory should be contacted and questioned. This is particularly important if the patient is receiving drugs structurally similar to the drug being tested. Cross-reactivity between the drug and the test can falsely increase test values. For example, therapeutic corticosteroids cross react with endogenous corticosteroid hormones, although the percentage of cross-reactivity varies with the assay and the drug. Some drugs cause cytotoxicity (e.g., aminoglycoside-induced nephrotoxicity); some stimulate changes without toxicity (e.g., glucocorticoid-induced alkaline phosphatase); and others interfere with hormones. There are many other ways drugs can interfere with diagnostic tests. The American Association of Clinical Pathologists publishes a handbook that summarizes changes in clinical pathology that might be drug induced. Access to this text or its information may be possible by contacting the appropriate diagnostic laboratory.

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4 Therapeutic Drug Monitoring

Dawn Merton Boothe

THERAPEUTIC DRUG MONITORING
WHY THERAPEUTIC DRUG MONITORING IS USED
WHEN THERAPEUTIC DRUG MONITORING SHOULD BE USED AND FOR WHICH DRUGS
HOW THERAPEUTIC DRUG MONITORING IS IMPLEMENTED
Impact of Drug Elimination Half-Life on Therapeutic Drug Monitoring
Single-Sample Versus Two-Sample Collection
Timing of Sample Collection
HOW THERAPEUTIC DRUG MONITORING SAMPLES SHOULD BE INTERPRETED
Information Needed for Therapeutic Drug Monitoring
Dose Modification with Kinetic Calculations
Dose Modification without Kinetics
WHERE THERAPEUTIC DRUG MONITORING IS OFFERED

THERAPEUTIC DRUG MONITORING

Therapeutic drug monitoring (TDM) is a tool that can help the clinician to determine an effective and safe dosing regimen for drug therapy for the individual patient. Monitoring can be used to confirm a plasma drug concentration (PDC) that is above or below the therapeutic range, thus minimizing the time that elapses before corrective measures can be implemented for the patient (Wilson, 1987; Neff-Davis, 1988; Pippenger and Massoud, 1984). Knowledge of the principles of drug disposition (see Chapter 1) and the factors that determine these principles in the individual patient (see Chapter 2) facilitates an understanding of the use of and the need for TDM.

WHY THERAPEUTIC DRUG MONITORING IS USED

The success of any fixed dosing regimen most often is based on the patient's clinical response to the drug. Fixed dosing regimens are designed to generate PDCs within a therapeutic range, that is, achieve the desired effect while avoiding toxicity. Recommended dosing regimens have proved most successful when based on scientific, pharmacokinetic studies performed in a population of normal, adult animals of the target species intended to receive the drug. Marked interindividual variability (within a species) has, however, been confirmed for many drugs (Arnsdorf, 1989; Ravis et al., 1984). More importantly, rarely does the patient receiving the drug meet the above criteria. Rather, the patient usually is diseased, and its illness often requires treatment with more than one drug.

The factors that determine drug disposition (see Chapter 2) are all amenable to change in the unhealthy patient. Physiologic, pathologic, and pharmacologic factors can profoundly alter the disposition of a drug such that therapeutic failure or, other adverse reactions occur (see Chapters 2 and 3). Changes in drug metabolism and excretion induced by age (Cowan et al., 1980), sex, disease (Atkins et al., 1989; Frazier and Riviere, 1987; Frazier et al., 1988; Dunbar et al., 1983), or drug interactions (Ravis 1984; Ravis 1987; Atkins/Snyder et al., 1988; DeRick 1981) are among the more important factors that can increase or decrease the expected PDC. Recommended dosing regimens are sometimes designed to compensate for the effects of some of these factors. Examples include many feline dosing regimens (e.g., for aspirin and some selected antimicrobials); the use of body surface area rather than body weight for drugs with a high potential of toxicity (e.g., anticancer drugs; see Chapter 1); and allometric scaling for exotic species. Unfortunately, the effects of many factors are unpredictable and cannot be anticipated in the individual patient, despite innovated dosing calculations.

If the patient's response to the drug is perceived as inappropriate due to either failure or toxicity, a trial and error approach can be used for modifying the dose. If subtherapeutic concentrations are suspected, the dose or frequency is empirically increased until an adequate response occurs. If a response is still not evident, the cycle may be repeated with a new drug or drug combination until all reasonable alternatives are exhausted, and the illness is then considered refractory to treatment. On the other hand, dosing regimens that induce toxic signs are decreased until the signs resolve, increasing the risk of therapeutic failure. Such a trial and error approach to dose modification is most appropriate when response to the drug can be easily measured. Examples include "to affect" drugs such as gas inhalants and ultrashort thiobarbiturate anesthetics, rapidly acting anticonvulsants such as diazepam, and lidocaine for the treatment of ventricular arrhythmias. Trial and error can also be used for illnesses that are not serious or do not require immediate resolution and for drugs characterized by large therapeutic windows, which are generally safe at high doses.

Trial and error modification of dosing regimens can, however, be inefficient and potentially dangerous when the drug response cannot be easily measured, the drug is characterized by a narrow margin of safety, or the patient's condition is life threatening. For example, lack of response to an antimicrobial agent might reflect bacterial resistance or simply failure to generate therapeutic antimicrobial concentrations. In life-threatening infections, timing of effective antimicrobial therapy is critical to success; likewise, toxicity must be avoided in a seriously ill patient. Although fever or white blood cell counts can be used to monitor the response to an antimicrobial drug in some patients, these parameters are not always abnormal before antimicrobial therapy and, in the case of life-threatening infections, may not change rapidly enough. Another example is that failure to control seizures with an antiepileptic drug may reflect the refractory nature of the seizures or PDCs that are subtherapeutic. The former is accompanied by a poorer prognosis and the latter should respond simply to an increase in PDC. In another example, differentiating an assumed digoxin-induced adverse reaction from clinical signs of cardiac or other disease is difficult if the PDC of digoxin is not known. Geriatric and pediatric patients represent age extremes for which TDM may prove beneficial (Gal, 1988).

WHEN THERAPEUTIC DRUG MONITORING SHOULD BE USED AND FOR WHICH DRUGS

Therapeutic drug monitoring is indicated in clinical situations in which an expected therapeutic effect of a drug has not been observed or in cases where drug toxicity due to a high toxic PDC is suspected. In addition, TDM can be used to establish whether optimum therapeutic drug concentrations have been achieved for drugs characterized by a response that is difficult to detect or when the manifestations of disease are life threatening and the trial and error approach to modification of the dosing regimen is unacceptable. When chronic drug administration is expected, TDM can be used to define the effective target PDC in the patient. The target PDC can then be used if pharmacokinetics change in the patient over the course of chronic drug administration due to disease, environmental changes, age, or drug interactions (e.g., phenobarbital). Drug monitoring has also been useful in identifying owner noncompliance as a cause of therapeutic failure or adverse reactions.

Drugs for which TDM is most useful are characterized by one or more of the following:

1. Serious toxicity coupled with a poorly defined or difficult to detect clinical end point (e.g., anticonvulsants and cyclosporine)
2. A steep dose-response curve for which a small increase in dose can result in a marked increase in desired or undesired response (e.g., theophylline; phenobarbital in cats)
3. A narrow therapeutic range (e.g., digoxin)
4. Marked interindividual pharmacokinetic variability that increases variability in the relationship between dose and PDC (e.g., phenobarbital)
5. Nonlinear pharmacokinetics that may lead to rapid accumulation of drugs to toxic concentrations (e.g., phenytoin or, in cats, phenobarbital)
6. An unexpected toxicity due to drug interactions (e.g., enrofloxacin-induced theophylline toxicity or chloramphenicol-induced or clorazepate-induced phenobarbital toxicity)
7. Cost that justifies confirmation of effective PDC in order to minimize dose and duration of therapy (e.g., cyclosporine)

In addition, TDM is indicated when a drug is used chronically (e.g., an anticonvulsant) and thus is more likely to induce toxicity or changes in pharmacokinetics or in a life-threatening situation (e.g., epileptic seizure or bacterial sepsis) in which a timely response is critical to the patient. Drugs for which TDM might not be indicated include those characterized by a wide therapeutic index and are seldom toxic even if PDCs are higher than recommended and those for which a response can be easily monitored by clinical signs.

Not all drugs can be monitored by TDM; certain criteria must be met (Abbott Laboratories, 1984). Patient response to the drug must correlate with (i.e., parallel) PDC. Drugs whose metabolites (e.g., diazepam) or for which one of two enantiomers comprise a large proportion of the desired pharmacologic response cannot be as effectively monitored by measuring the parent drug (Drayer, 1988). Rather, all active metabolites, the parent drug, or both should be measured. Species differences vary in the production of these metabolites. For example, the efficacy of primidone as an anticonvulsant in dogs and cats reflects its conversion to phenobarbital. Thus phenobarbital is measured. In people, procainamide is metabolized to an active metabolite. Although dogs are deficient in this metabolite, the parent compound and the active metabolite must be measured.

An effective therapeutic (C_{min}) or toxic (C_{max}) range must have been identified for the drug in the species and for the disease being treated (Arnsdorf, 1989). For most drugs, recommended therapeutic ranges in animals have been extrapolated from those determined in humans. Controlled clinical trials that establish therapeutic ranges for various diseases generally have not been performed with animals. Yet, therapeutic ranges in the various animal species may differ from those of people and from one another. Procainamide is an example whose ranges might differ. Bromide offers another example: Concentrations above 1.5 mg/mL might be considered toxic in people but are at the low to mid therapeutic range in epileptic dogs. Also, the therapeutic range may differ for the desired response (i.e., indication). Ideally, the pharmacokinetics of the drug have been established in a large population of animals to receive the drug so that normal ranges are available for the predictive pharmacokinetic parameters.

The drug must be detectable in a relatively small serum sample size, and analytical methods must be available to rapidly and accurately detect the drug in plasma (Price, 1984). The methods must be specific for the drug and be able to differentiate it from other compounds of interest, including metabolites of the drug if appropriate, or measure drug and active metabolites if appropriate. The cost of the analytical method must be reasonable. Drugs that meet these criteria and for which TDM has proved useful in veterinary medicine include selected anticonvulsants (phenobarbital, primidone, potassium bromide, selected benzodiazepines), antimicrobials (e.g., aminoglycosides, gentamicin, and amikacin); cardioactive drugs (digoxin, procainamide, lidocaine, and quinidine); and theophylline (Table 4–1). Cyclosporine, an immunomodulating drug, has just recently begun to be monitored; behavior-modifying drugs (e.g., amitriptyline) may join the list as more is learned about these drugs in animals.

CASE 1 ▼

THERAPEUTIC FAILURE DUE TO PHENOBARBITAL INDUCTION OF DRUG METABOLIZING ENZYMES

Signalment:	3.5-year-old male Labrador retriever		
Chief Complaint:	Seizures		
Pertinent History:	A diagnosis of epilepsy was made 6 months before presentation. Patient was suffering from severe cluster seizures. There was an initial response to phenobarbital, but seizures occurred again 6 months into therapy.		
Drug of Interest:	Phenobarbital		
Concern:	Efficacy		
Other Drugs:	None		
Dosing Regimen:	4.1 mg/kg every 12 hours orally		
Duration of Current Regimen:	6 months. Phenobarbital concentrations at 3 months (baseline) were 35 μg/mL (peak) and 31 μg/mL (trough). Elimination half-life at that time was 40 hours.		
Patient Response:	Seizure control initially improved, and there was no evidence of grogginess. The patient suffered a series of cluster seizures this weekend. The referring veterinarian was interested in adding an alternative anticonvulsant (e.g., bromide).		
Drug Concentration:	18 μg/mL 15 μg/mL	**Time:**	5 hours 12 hours
Drug Elimination Half-Life:	27 hours	**Volume of Distribution:**	NA
Predicted Peak:	NA	**Predicted Trough:**	NA
Recommendation:	Increase phenobarbital dose to 7.5 mg/kg every 12 hours (4.5 mg/kg × 30 μg/mL per 18 μg/mL), targeting a peak concentration of 30 μg/mL. Retest at new steady state (which will take only 3 to 5.5 days in this patient).		
Comments:	Phenobarbital concentrations decreased in this patient by close to 50% without a decrease in dose. The elimination half-life decreased by 50%. The decrease most likely reflects induction of drug metabolizing enzymes by phenobarbital, resulting in increased clearance and decreased drug concentrations. Induction occurs in most animals and should be anticipated by using a sufficiently high starting dose (2 mg/kg) for phenobarbital and measuring drug concentrations at steady state (approximately 2 weeks after therapy is begun) and then again at 3 months.		
Follow-Up:	The dose was increased to 6.5 mg/kg. Drug concentrations 1 month later were 33 mg/mL (peak) and 29 mg/mL (trough). The patient has been seizure free for 6 months. Although bromide therapy could have been started in this patient, the increase in phenobarbital concentration was easier and as effective, leaving bromide available should this patient's disease get worse.		

HOW THERAPEUTIC DRUG MONITORING IS IMPLEMENTED

Impact of Drug Elimination Half-life on Therapeutic Drug Monitoring

In general, TDM should not be performed until PDCs have reached steady state in the patient. Steady-state PDCs occur at the point when drug input and drug elimination (i.e., metabolism, excretion, or both) are equilibrated (see Chapter 1). Although PDCs change to some degree during the dosing interval, they remain constant between intervals at steady state (Fig. 4–1). With multiple drug dosing, PDCs will reach 50% of their steady-state concentration at one half-life, 75% at two half-lives, 87.5% at three half-lives, and so on. Thus, regardless of the drug, steady-state concentrations are attained only after four to five half-lives of a drug administered according to a fixed dosing regimen. The same time period (i.e., four to five drug half-lives) must elapse for steady-state plasma drug concentrations to be reestablished if any portion of the original dosing range (i.e., dose, frequency, or route) is changed. Evaluation of a drug's efficacy is often inappropriate until steady state has been reached because it is only then the maximum peak and trough drug concentrations and, thus, maximal response will have been achieved.

As can be seen from Table 4–1, the time that must elapse from the start of the dosing regimen until monitoring can take place is quite variable. Depending on the drug half-life in the normal population sample, this time ranges from less than 1 day to more than 3 months. For drugs with a long half-life compared with the dosing interval, drug accumulation can be very dramatic (i.e., the drug concentrations after the first dose are much lower than the drug concentrations at steady state). The dosing regimen

Table 4–1. Therapeutic Drug Monitoring Data for Drugs Monitored in Small Animals

Drug	Usual Dosage	Interval (Hours)	Therapeutic Range*	Volume of Distribution (L/kg)	Elimination Half-Life	Time to Steady State	Sample Collection Peak	Sample Collection Trough
Amikacin	7–20 mg/kg	12–24	2–25 μg/mL†	0.25	1–2 h	1 day	1 h (plastic only)	2 half-lives (3–6 h)‡
Aspirin								
Dog	10 mg/kg	8–12	50–100 μg/mL	0.19	8 h	40 h	2–4 h	BND
Cat	10 mg/kg	72		0.19	38 h	8 days		
Benzodiazepines	1–2 mg/kg		100–200 ng/mL§		<8 h	1 day	2–5 h	BND‡
Bromide	15–20 mg/kg	12–24	1.0–3.5 μg/mL		24 days	2–3 months‖		BND
Cyclosporine	High: 6–8.5 mg/kg	12	Trough about 400–600 ng/mL (100–300 ng/mL may be sufficient for perianal fistulas)		1.3¶	5.6**	2–4 h	BND
	Moderate: 3.5–5.5 mg/kg	12						
	Low: 0.75–3 mg/kg	12						
Digoxin								
Dog	0.011 mg/kg	12	0.9–3.0 ng/mL	19	31.3 h	7 days	Toxicity: 2–5 h†† (glass only)	Efficacy: BND
Cat	0.008 mg/kg	12–24	0.9–2.0 ng/mL	14.5	33.5 h	7 days		
Gentamicin								
Dog	2–8 mg/kg	12–24	0.5–1.5 μg/mL†	0.3–0.4	0.9–1.3 h	6.5 h	1 h (plastic only)	2 half-lives (3–6 h)
Cat	2–8 mg/kg	12–24	5.0–8.0 μg/mL					
Phenobarbital (dog)	2 mg/kg	12	14–45 μg/mL	0.7	32–75 h	14–16 days	4–5 h‡‡	BND
Primidone								
Dog	11–25 mg/kg	12–24	Based on phenobarbital	0.7	6.1 h	14–16 days	4–5 h‡‡	BND
Cat	11–20 mg/kg							
Procainamide (dog)	15 mg/kg	12	—**	1.4–2.1	2.9 h	15 h	2–4 h	BND
Quinidine								
Dog	6–20 mg/kg		2.5–5.0 μg/mL	2.9	5.6 h	28 h	2–4 h	BND
Cat	Not recommended			2.2	1.9 h	10 h		
Theophylline	7–11 mg/kg	8–12 (D)	10–20 μg/mL	0.82	5.7 h	29 h	1–2 h§§	BND
	4 mg/kg	12–24 (C)		0.46	7.9 h	40 h		
Thyroid hormones T_3, T_4	T_3: 4–6 μg/kg (D), 4.4 μg/kg (C) T_4: 20 μg/kg (D), 50–100 μg/kg (C)		0.8–1.5 μg/mL (D) 1.5–3.5 μg/mL (D) 1.5–5.0 μg/mL (C)		5–6 h (D) 12–15 h (D)	<24 h‖‖ 2–3 h (D)	4–5 h	BND

Abbreviations: BND = before next dose (trough); C = cat; D = dog.

*Therapeutic ranges are extrapolated from human patients unless noted otherwise. Note that ranges may also vary with the laboratory and specifically with the instrumentation used to assay the drug of interest. Values in this table may be superseded if the values for the instrument have been validated appropriately. Because sample sizes and assay methods vary, the specific laboratory that will be performing the assay should be contacted regarding sample volume, proper collection tubes, need for refrigeration, and other sample handling specifics as well as "normal" ranges.

†"Target" peak concentration for aminoglycosides depends on infecting organism and specifically on the minimum inhibitory concentration (MIC) of the infecting organism. The target peak concentration should be 4 to 10 times the MIC. Trough concentration should be equal to or below that recommended in order to minimize toxicity.

‡For drugs with a very short half-life, trough sample may no longer have detectable drug. Wait one or two predicted elimination drug half-lives between peak and trough sample collections.

§600 ng/mL listed for humans. Assay should measure all benzodiazepines (parent and active metabolites) relative to dosing interval.

‖Single sample postload and 3 to 4 weeks later or 3 to 4 weeks into therapy if a loading dose not used is recommended as therapy is begun to allow pro-active monitoring.

¶For people; data not available for dogs.

**As suggested by Papich.

††Both peak and trough recommended because of short half-life; single peak acceptable if toxicity is a concern.

‡‡Peak and trough recommended if seizures are difficult to control.

§§For slow-release preparations, one sample may be sufficient.

‖‖Monitoring should not take place until the body has had a chance to physiologically adapt to drug therapy (i.e., 4 to 6 weeks after therapy is implemented).

Values for ranges of thyroid hormones reflect a radioimmunoassay. Values are likely to be different for each laboratory. Contact the laboratory, or, if doing assays in house, establish in-house normal ranges. Overlap between normal and abnormal is great, regardless of the laboratory, and interpretation should be based on clinical signs.

of such drugs is designed so that drug concentrations will be in the therapeutic range, but only when steady state concentrations have been achieved.

Attention to steady state is important for drugs that accumulate with repetitive dosing. For such drugs, the peak PDC is higher at steady state than after the first dose. At steady state, the magnitude of increase in PDC at steady state compared with that after the first dose is referred to as the *accumulation ratio* (see Chapter 1 and Fig. 4–2). The amount that the drug accumulates depends on how much longer the half-life is than the dosing interval (see Table 1–1). A drug whose half-life is equal to its dosing interval accumulates twofold (i.e., at steady state, peak PDCs will be twice what they were after the first dose).

For drugs characterized by a long half-life, TDM can be used during the first dose to predict peak and trough PDC at steady state by multiplying peak and trough PDCs after the first dose by the assumed accumulation ratio (based on the reported drug elimination half-life or that measured in the patient from peak and trough concentrations and on the dosing interval). Prediction is accurate only if the reported elimination half-life represents that in

CASE 2 ▼

PHENOBARBITAL-CHLORAMPHENICOL DRUG INTERACTION

Signalment:	3.5-year-old male German shepherd		
Chief Complaint:	Acute onset of depression, anorexia, and lethargy		
Pertinent History:	A diagnosis of epilepsy was made, 1 year before presentation. The patient was suffering from severe cluster seizures. The response to phenobarbital was initially acceptable, but seizures worsened and potassium bromide was added to the regimen 3 weeks before presentation. The response to combination therapy was acceptable. The patient presented for cough 1 week before presentation. Lower respiratory infection was diagnosed and antibiotic therapy begun. Three days later, the patient presented for the chief complaint. Vital signs on physical examination are normal. Clinical laboratory tests are normal. Phenobarbital 1 week before presentation was 32 μg/mL (not certain if a peak or trough sample).		
Drug of Interest:	Bromide		
Concern:	Toxicity		
Other Drugs:	Phenobarbital 4 mg/kg every 12 hours orally (at current dose for 2 weeks; last phenobarbital collected was at steady state with the current dosing regimen); chloramphenicol 25 mg/kg every 8 hours for 3 days		
Dosing Regimen:	A 450 mg/kg loading dose measured 6 months before presentation was 0.9 mg/mL. The maintenance dose was 10 mg/kg every 12 hours. The maintenance dose was increased to 15 mg/kg every 12 hours, but concentrations were not subsequently remeasured at steady state.		
Duration of Current Regimen:	Bromide, 6 months; phenobarbital 1 year; chloramphenicol, 4 days		
Patient Response:	Seizure control was improved. Patient was not groggy until recent episode.		
Drug Concentration:	2.10 μg/mL	**Time:**	12 hours
Drug Elimination Half-Life:	NA	**Volume of Distribution:**	NA
Predicted Peak:	NA	**Predicted Trough:**	NA
Recommendation:	Bromide concentrations are not sufficiently increased to cause clinical signs. Phenobarbital concentrations were measured: Peak concentration was 50 μg/mL; trough concentration was 46 μg/mL. Phenobarbital elimination half-life was 58 hours.		
Comments:	This patient was presented for presumed bromide toxicity. The bromide concentrations were not, however, consistent with the profound depression the patient was exhibiting. Phenobarbital concentrations were checked to identify a possible contribution to lethargy in a sample of blood collected just before the onset of chloramphenicol therapy. Phenobarbital concentrations had indeed increased in this patient by 40% to 50% despite no dose change. The increase was presumed to be due to chloramphenicol therapy. Chloramphenicol is a potent inhibitor of drug metabolizing enzymes, resulting in decreased phenobarbital clearance. Drug elimination half-life had not been previously determined for phenobarbital in this patient, so a change in half-life could not be documented.		
Follow-Up:	Chloramphenicol therapy was discontinued. Phenobarbital therapy was discontinued for one drug elimination half-life and then restarted at the same dose. Within 48 hours, the patient was normal.		

the patient. Using this approach, the dose can be modified proactively (i.e., before steady state occurs). Drugs for which this might be beneficial include phenobarbital (half-life up to 5 days; steady state occurring at 2 to 3 weeks) and bromide (half-life 24 days; steady state occurring at 2 to 3 months). More useful might be measuring concentrations at approximately one drug half-life (e.g., 1 month for bromide) in order to estimate PDCs at steady state. Concentrations collected at this time are approximately 50% of what they will be at steady state.

A third alternative to proactive monitoring is available for patients for whom steady-state concentrations must be reached immediately. A loading dose (see Chapter 1) can be administered to rapidly achieve therapeutic PDC (see Fig. 4–1). The loading dose (Figs. 4–1B and 4–2) needed to achieve a known therapeutic concentration of a drug depends on the volume of distribution (Vd) of that drug in the patient and the target (i.e., the therapeutic concentration; see Table 4–1). If the drug is orally administered, the bioavailability (F) must also be taken into account when the dose is determined. Although a loading dose can decrease the time for maximum response to occur to a drug (by avoiding accumulation to steady state), the hazard of an adverse reaction to the drug is much greater. Thus, loading doses are not advised for drugs characterized by a narrow therapeutic index and that tend to cause undesirable

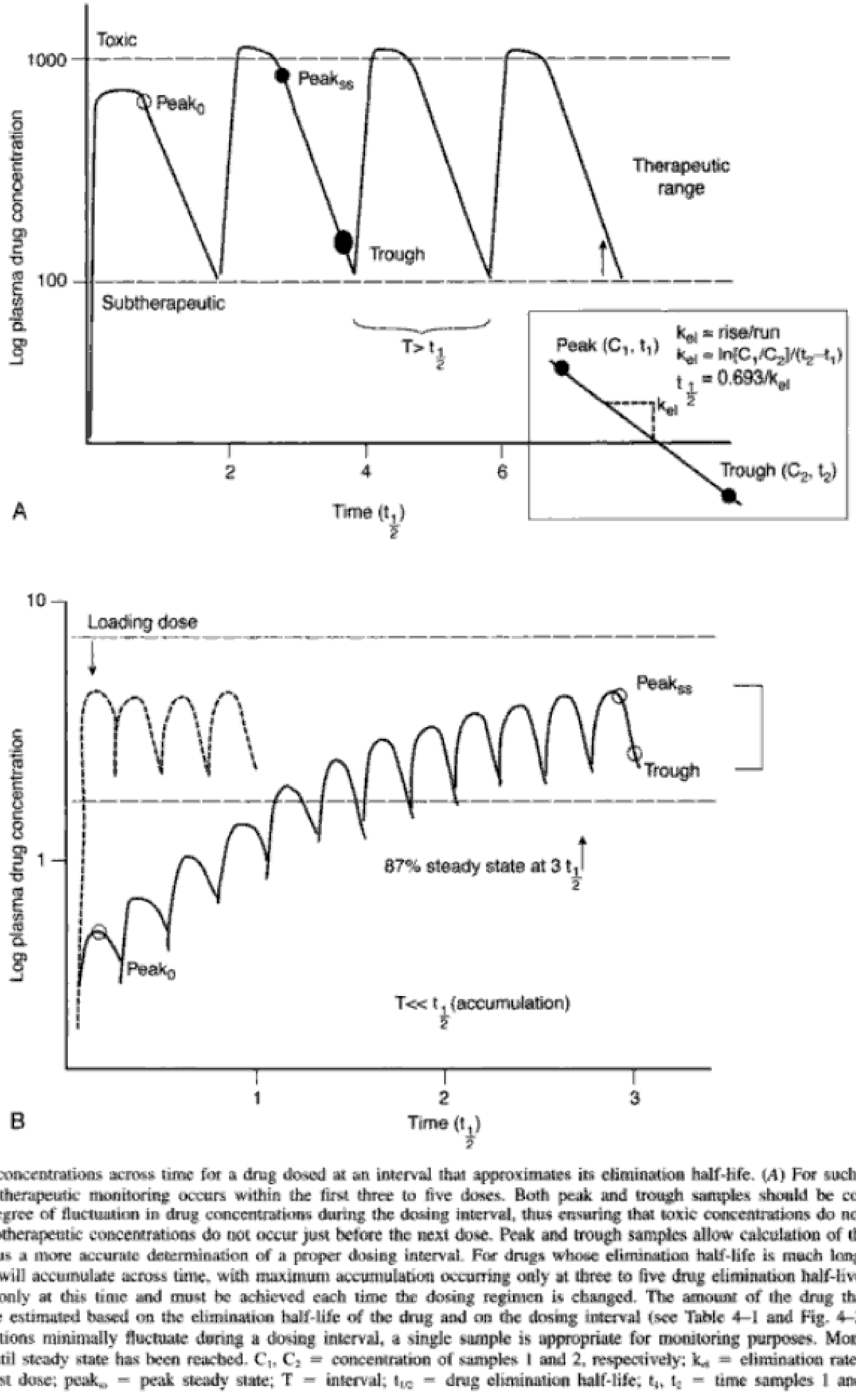

Figure 4–1. Drug concentrations across time for a drug dosed at an interval that approximates its elimination half-life. (*A*) For such drugs, response to therapy and thus therapeutic monitoring occurs within the first three to five doses. Both peak and trough samples should be collected in order to characterize the degree of fluctuation in drug concentrations during the dosing interval, thus ensuring that toxic concentrations do not occur as the drug peaks and that subtherapeutic concentrations do not occur just before the next dose. Peak and trough samples allow calculation of the elimination half-life (*inset*) and thus a more accurate determination of a proper dosing interval. For drugs whose elimination half-life is much longer than the dosing interval, the drug will accumulate across time, with maximum accumulation occurring only at three to five drug elimination half-lives (*B*). Steady state will be achieved only at this time and must be achieved each time the dosing regimen is changed. The amount of the drug that is anticipated to accumulate can be estimated based on the elimination half-life of the drug and on the dosing interval (see Table 4–1 and Fig. 4–2). For such drugs, because concentrations minimally fluctuate during a dosing interval, a single sample is appropriate for monitoring purposes. Monitoring should not, however, occur until steady state has been reached. C_1, C_2 = concentration of samples 1 and 2, respectively; k_{el} = elimination rate constant; peak$_0$ = peak following first dose; peak$_{ss}$ = peak steady state; T = interval; $t_{1/2}$ = drug elimination half-life; t_1, t_2 = time samples 1 and 2 were collected, respectively.

CASE 3 ▼

DIGOXIN-INDUCED TOXICITY; LONG ELIMINATION HALF-LIFE

Signalment:	6-year-old male dachshund cross		
Chief Complaint:	Congestive heart failure; renal failure		
Pertinent History:	The patient has been receiving digoxin therapy for 6 months. Within the last 3 months, renal disease has become decompensated. The day before presentation, the patient vomited and became ataxic and disoriented. Patient blood urea nitrogen is 82 mg/dL, and creatinine is 1.57 mg/dL.		
Drug of Interest:	Digoxin		
Dosing Regimen:	0.005 mg/kg every 12 hours orally		
Duration of Current Regimen:	90 days		
Concern:	Safety		
Other Drugs:	Enalapril, furosemide, thyroxine		
Drug Concentration:	2.40 ng/mL 2.47 ng/mL	**Time:**	2 hours 12 hours
Drug Elimination Half-Life:	>52 hours	**Volume of Distribution:**	NA
Predicted Peak:	NA	**Predicted Trough:**	NA
Recommendation:	Concentrations are at the upper end of the therapeutic range and are not necessarily consistent with toxicity, but a decrease in dose by about 20%, targeting 2.0 ng/ml, would be prudent. Clinical signs of uremia cannot be distinguished from clinical signs of digoxin toxicity. Prolonging the interval to at least 24 hours also would be appropriate. Collecting a peak and 24-hour trough concentration would be indicated to determine the proper dosing interval.		
Comments:	The prolonged half-life for digoxin in this patient presumably reflects decompensated renal disease. Note that both a peak and a trough sample were helpful in establishing the prolonged drug elimination half-life. Without both samples, the duration of the half-life and the magnitude of decreased clearance could not have been appreciated (see Case 4). Should the patient respond to therapy for its renal disease and digoxin elimination improve, monitoring is again indicated to establish a new dosing regimen because drug half-life is likely to decrease.		
Follow-Up:	NA		

adverse reactions (e.g., digoxin). For safe drugs (e.g., bromide, phenobarbital), however, a loading dose can be administered if deemed appropriate. Note, however, that even if a loading dose is administered, the maintenance dose may be either too high or too low; the need for maintenance dose modification may not become evident until steady state occurs (i.e., at three to five drug half-lives). Monitoring can, however, be used to proactively (at one drug half-life) evaluate the proper maintenance dose.

When using a loading dose (e.g., for bromide), TDM should be performed three times. The first time is after oral absorption of the last dose of the loading dose is complete to establish a baseline. The second time would be at one drug half-life later (e.g., at 24 to 30 days for bromide) to ensure that the maintenance dose is able to maintain concentrations achieved by loading. Collection of the second sample one drug half-life later is recommended because most of the change in drug concentrations that will occur if the maintenance dose is not correct will occur during the first half-life. If the second sample (collected at one drug half-life) does not approximate the first (collected immediately after the load), the maintenance dose can be modified at this time rather than wait for steady state with the risk of therapeutic failure or toxicity. The third time to monitor bromide would be at steady state (e.g., 3 months) to establish a new baseline.

Many drugs are characterized by half-lives that are much shorter than the dosing interval. For these drugs, no to little accumulation occurs, the concept of "steady state" is perhaps irrelevant, and response can be evaluated with the first dose (or as soon as the disease has had time to respond). For example, many antimicrobials (e.g., aminoglycosides) are characterized by a half-life that is less than 2 hours (e.g., amikacin in dogs) but are given at a dosing interval of 8 to 12 hours (Neff-Davis, 1988). Thus four to six drug half-lives will have elapsed, and less than 5% of the dose will remain in the body by the next dose. With this dosing regimen, amikacin does not accumulate in the plasma, and a "steady-state equilibrium" will not be reached. Even though drug concentrations drop below C_{min} for many of these drugs, the effects of the drug are often still present. For example, aminoglycoside antibiotics are still effective because the postantibiotic effect exhibited by this and many other antimicrobials allows a relatively long (and convenient) dosing interval to be used despite the short drug half-life (Bundtzen et al., 1981). Therapeutic

CASE 4 ▼

DIGOXIN THERAPY: RESPONSE AND SHORT HALF-LIFE

Signalment:	8-year-old female hound cross		
Chief Complaint:	Congestive heart failure due to mitral insufficiency		
Pertinent History:	The patient has been receiving digoxin therapy for 8 days. Patient has responded to therapy and is showing no evidence of toxicity.		
Drug of Interest:	Digoxin		
Dosing Regimen:	0.008 mg/kg every 12 hours orally		
Duration of Current Regimen:	8 days		
Concern:	Baseline check		
Other Drugs:	Enalapril, furosemide, phenylbutazone, and chlorpheniramine		
Drug Concentration:	2.88 ng/mL 1.42 ng/mL	**Time:**	1.25 hours 9 hours
Drug Elimination Half-Life:	8 hours	**Volume of Distribution:**	NA
Predicted Peak:	NA	**Predicted Trough:**	NA
Recommendation:	Concentrations are above the upper end of the therapeutic range, but, with no evidence of toxicity, the dose should not necessarily be changed. With a 12-hour half-life, the dosing interval should not be prolonged (and could be reduced to an 8-hour dosing interval with the same total daily dose). Leave dosing regimen as is or decrease dose by 10%.		
Comments:	Compare the drug half-life in this patient with the reported normal (24 hours) and with that in Case 3. Had a single sample been collected halfway through the dosing interval, concentrations would have been in the lower end of the therapeutic range and the dose may have been inappropriately increased. The half-life in this patient indicates that the dosing interval should not be longer than 12 hours. Should a 24-hour dosing interval be used, trough drug concentrations would approximate 0.35 ng/mL.		
Follow-Up:	NA		

drug monitoring is useful during treatment with these drugs to ensure that therapeutic concentrations are achieved and that toxic concentrations are avoided during each dosing interval. Note, however, that if a "trough" sample is collected just before the next dose, drug concentrations may not be detectable. Thus, the trough sample for such drugs should be collected at 2 to 3 drug half-lives after administration (see Case 6).

Single-Sample Versus Two-Sample Collection

The number of samples collected for TDM depends on the drug, its elimination half-life, and the question to be answered by monitoring (i.e., is the dose safe, or is it effective?). For all drugs, PDCs are likely to continue to fluctuate during a fixed dosing interval unless drug half-life is much longer than the dosing interval. The trough PDC is the lowest drug concentration that develops during a dosing interval (see Fig. 4–1), and it theoretically should not drop below the C_{min} (the aminoglycosides are one exception). It occurs just before administration of the next dose and represents the maximum effect of the processes of drug elimination (i.e., metabolism and excretion) that occur between doses. The peak PDC is the maximum concentration achieved after a dose is administered, and presumably it should not exceed C_{max}. For intravenous (IV) drugs, its magnitude is based on the Vd; for oral drugs, its magnitude also depends on the rate and extent of drug absorption (i.e., bioavailability). Predicting when the highest drug concentration occurs following IV or oral administration is less successful than predicting when trough concentrations occur.

The relationship between peak and trough PDCs is determined by drug half-life. Peak and trough concentrations are very different from one another for drugs with a short half-life compared with the dosing interval (e.g., benzodiazepines, antibiotics, and, for some patients, phenobarbital). For such drugs, both a peak and a trough sample should be collected. Collection of at least two samples during a single dosing interval is particularly important for drugs characterized by a narrow therapeutic range. For these drugs, effective and toxic drug concentrations are not widely separated, and such drugs are more likely to cause adverse reactions.

In contrast to drugs with a short half-life, peak and trough concentrations do not differ substantially for drugs whose half-life is much longer than the dosing interval (e.g., bromide, and, for some patients, phenobarbital), and a single sample is generally sufficient for such drugs. Single samples might also be indicated for slow-release

Formulas for calculating dosing regimens

Elimination rate constant:	$k_{el} = \ln (C_1/C_2)/(t_2 - t_1)$
Drug elimination half-life	$t_{\frac{1}{2}} = 0.693/k_{el}$
Maximum time that can lapse between doses:	$T_{max} = \ln(C_{max}/C_{min})/k_{el}$
Amount of drug to be administered during a dosing interval:	$D_{M,max} = (Vd/F) \cdot (C_{max} - C_{min})$
Dose per unit time:	$D_{M,max}/T_{max}$
Dose each interval:	$\frac{D_{M,max} \cdot \text{Interval}}{T_{max}}$
Loading dose:	$DL = (Vd/F) \cdot C_{ss,max}$
Accumulation ratio:	$1/(1-[\frac{1}{2}]^{Z})$ or $1/1-e^{T/t_{\frac{1}{2}}}$

Figure 4–2. The data necessary for calculating dosing regimens can be obtained from therapeutic drug monitoring and from values reported in the literature, as modified (e.g., the volume of distribution) for the patient. C_1, C_2 = concentration of samples 1 and 2, respectively; C_{max} = maximum PDC (peak); C_{min} = minimum PDC (trough); $C_{ss,max}$ = maximum (target) PDC at steady state (mg/mL); F = bioavailability (100% if intravenous); In = interval; K_{el} = elimination rate constant; PDC = plasma drug concentration; t_1, t_2 = time samples 1 and 2 were collected, respectively; Vd = volume of distribution (L/kg); Z = $T/t_{\frac{1}{2}}$ (interval [T]/half-life [$t_{\frac{1}{2}}$]).

products (e.g., theophylline) because constant drug absorption often mitigates a detectable difference between peak and trough concentrations. Single samples also can be collected after a loading dose (i.e., bromide) or at the first half-life (i.e., 3 to 4 weeks) from a patient that has just begun bromide therapy. Finally, if the question to be answered by TDM is one of toxicity (e.g., for digoxin or phenobarbital), or efficacy throughout the dosing interval, then a single peak or trough sample may answer the question, although this approach may be less ideal.

Often, whether or not the half-life is short or long can only be determined by collecting both a peak and a trough sample. For phenobarbital, the elimination half-life may initially be longer than the dosing interval (i.e., more than 48 hours), but after induction (i.e., several months into therapy) it may be much shorter (i.e., less than 12 hours) in the same patient (see Case 1). The need for peak and trough samples may not be evident if a long half-life is anticipated. A prudent approach for patients beginning phenobarbital therapy would be to collect peak and trough samples as a baseline but single samples for rechecks if the patient is responding well to therapy. Peak and trough samples should be collected from any patient that is not responding well to therapy with any drug that may have a short half-life compared with the dosing interval. Digoxin provides a good example of the risk associated with collecting only a single sample when assessing efficacy. Digoxin is characterized by a half-life that ranges from less than 12 hours, thus allowing concentrations to become subtherapeutic during a dosing interval, to more than 36 hours (particularly in patients with renal disease) (see Case 3). The half-life can change again if the patient responds to therapy for cardiac failure. If toxicity is suspected, a single sample collected at the time that clinical signs of toxicity occur can confirm toxicity. Neither toxicity nor efficacy can be confirmed throughout the dosing interval, however, unless two samples (peak and trough) are collected (see Case 4).

If a kinetic profile of a patient is the reason for TDM, at least two samples must be collected to establish a PDC versus time curve. The samples preferably are collected at the peak and trough times unless the interval is so long that drug may not be detectable at the trough time period (i.e., aminoglycosides administered at 12- or 24-hour dosing intervals). The most accurate kinetic information is generated from patients receiving an IV dose because the Vd can be estimated along with drug elimination half-life. For oral doses, only the rate of elimination and the drug half-life can be obtained.

Timing of Sample Collection

Trough samples are generally recommended for consistency across time if single samples are to be collected. Trough samples should be collected close to but before a dose. Time of peak PDC is more difficult to determine. Peak PDC should be determined after drug absorption and distribution are complete (see Chapter 1). The route of drug administration can influence the time at which peak PDCs occur, which vary among drugs. For orally administered drugs, absorption is slower (1 to 2 hours), and distribution is often complete by the time peak PDCs have been achieved.

The absorption rate can, however, vary widely due to factors such as product preparation, the effect of food, or patient variability. Obviously, a drug prepared as an elixir will be absorbed more rapidly than the same drug prepared as a capsule or tablet. Because food can slow the absorption of many drugs, fasting is generally indicated (if safe) before TDM. Generally, peak PDCs occur 1 to 2 hours after oral administration. Some drugs are simply absorbed more slowly than others (e.g., phenobarbital), and the time of peak PDC sample collection is longer (e.g., 2 to 5 hours for phenobarbital). For drugs administered intravenously, absorption is not a concern, but distribution is. For some intramuscular and subcutaneous administrations, absorption occurs rapidly (i.e., 30 to 60 minutes), but, again, drug distribution may take longer. Thus, PDCs generally are measured 1 to 2 hours after parenteral drug administration. Exceptions must be made for drugs, such as digoxin, for which distribution may take 6 to 8 hours. Samples should not be collected for these drugs until distribution is complete (see Table 4–1).

HOW THERAPEUTIC DRUG MONITORING SAMPLES SHOULD BE INTERPRETED

Information Needed for Therapeutic Drug Monitoring

The minimum information necessary for interpretation of PDCs includes the following:

1. The total daily dose of drug that will be correlated with the patient's measured PDC is important. The patient's

PDC is then compared with the target concentration, and the dose is modified proportionately.

2. Time intervals of drug administration are particularly important for drugs with short half-lives (e.g., aminoglycosides). Provision of this information ensures the clinical pharmacologist that blood samples contain the actual trough or peak drug concentration. From these data, a drug half-life can be calculated and a proper dosing interval can be determined.

3. The patient's clinical status is important because both acute and chronic diseases can dramatically alter drug disposition patterns. This is particularly true for patients with renal, hepatic, or cardiac disease. If this information is lacking, disease-induced changes in drug disposition cannot be distinguished from other causes such as noncompliance or drug interactions, nor can appropriate recommendations be made regarding dosing modifications.

4. Concurrently administered drugs may alter drug disposition patterns and thus contribute to individual differences in drug disposition. Frequency, dose, amount, and the actual times of all drugs given to the patient must be known in order to recognize or predict potential drug interactions.

5. Physiologic characteristics such as patient species, breed, and age are often important to the interpretation of the PDC because known or predictable differences may induce drug disposition and because there may be known differences in pharmacodynamic responses. Weight must be known in order to determine Vd for IV drugs.

6. The reason for TDM should be given, i.e., has the patient failed therapy or is the patient exhibiting signs of toxicity?

It is important to remember that the therapeutic range is a population parameter and reflects the range between which 95% of the animals might respond. Where in the therapeutic range the individual animal responds is to be determined by TDM. Concentrations must be evaluated in the context of the clinical patient. Some animals may respond below the therapeutic range. Thus, the absence of

CASE 5 ▼

THEOPHYLLINE-ENROFLOXACIN DRUG INTERACTION

Signalment:	6-year-old male neutered collie		
Chief Complaint:	Hyperactivity. Allergic rhinitis has been present for 2 months. There is radiographic evidence of lung-lobe consolidation, and clinical signs are compatible with pneumonia developed 1 week before presentation.		
Pertinent History:	Theophylline therapy begun 3 days before presentation. The patient began exhibiting signs of hyperactivity and restlessness 24 hours before presentation.		
Other Drugs:	Enrofloxacin 2.5 mg/kg every 12 hours orally (begun at the same time as theophylline); prednisolone 1 mg/kg every 48 hours		
Drug of Interest:	Theophylline		
Concern:	Toxicity		
Dosing Regimen:	21 mg/kg orally every 12 hours (slow-release product)		
Duration of Current Regimen:	3 days		
Patient Response:	Restlessness, pacing, irritability		
Drug Concentration:	47 μg/mL 31 μg/mL	**Time:**	12 hours 24 hours
Drug Elimination Half-Life:	19 hours	**Volume of Distribution:**	NA
Predicted Peak:	Approximately 65 μg/mL	**Predicted Trough:**	NA
Recommendation:	Decrease the dose by half or decrease the dose by 25% and prolong the dosing interval by 12 to 24 hours. Retest at the new steady state (in 3 days) and at discontinuation of enrofloxacin		
Follow-Up:	After monitoring, the dosing interval was prolonged to 24 hours, and the dose was decreased by 50% from 20 to 10 mg/kg. A recheck revealed a peak and trough concentration of 12.3 μg/mL and 10.3 μg/mL at 2 and 22 hours, respectively. Near subtherapeutic concentrations indicated that either the dose must be increased or the interval decreased to 12 hours.		
Comments:	The fluorinated quinolones can increase concentrations of theophylline when the two drugs are given simultaneously. The mechanism is presumed to be due to impaired drug metabolism by enrofloxacin with subsequent decreased theophylline clearance. This drug interaction is well established for ciprofloxacin in people and has been documented for enrofloxacin as well. The drug elimination half-life of theophylline in this patient while receiving enrofloxacin was 19 hours, which is twice that expected in dogs.		

CASE 6 ▼

AMINOGLYCOSIDE AND INTENSIVE FLUID THERAPY

Signalment:	2-year-old male intact Staffordshire terrier		
Chief Complaint:	Peritonitis and bacteremia secondary to prostatic abscess		
Pertinent History:	Surgical correction of prostatic abscess; drug samples collected 24 hours postoperatively		
Other Drugs:	Antiemetics (metoclopramide); intensive fluid therapy (balanced crystalloid)		
Drug of Interest:	Gentamicin		
Concern:	Efficacy and safety		
Dosing Regimen:	4 mg/kg IV every 24 hours		
Duration of Current Regimen:	24 hours		
Patient Response:	Febrile, nonresponsive		
Drug Concentration:	5.34 μg/mL 0.73 μg/mL	**Time:**	2 hours 9 hours
Drug Elimination Half-Life:	2.4 hours	**Volume of Distribution:**	0.45 L/kg
Predicted Peak Concentration:	10 μg/ml	**Trough Concentration:**	Nondetectable
Recommendation:	Double the dose to target 20 μg/mL (assuming a minimal inhibitory concentration of 1 to 2 μg/mL) and maintain current 24 hour dosing interval.		
Follow-Up:	The patient's condition remained critical for 2 more postoperative days but then began progressive improvement. The patient was discharged 10 days postoperatively.		
Comments:	Actual peak gentamicin concentration was lower than expected (expected: 10 μg/mL), presumably due to intensive fluid therapy. The reported volume of distribution for gentamicin in dogs is 0.25 L/kg, but it was 0.45 L/kg in this patient. Gentamicin is distributed to extracellular fluid, which was probably increased in this patient by fluid therapy. A nearly doubled distribution volume resulted in a near halving of peak concentrations. The drug elimination half-life in this patient is 2.4 hours, which is normal. Doubling of the dose will add only one drug half-life to the time that target trough concentrations (<1 μg/mL) will be reached, which currently occurs by 9 hours in this patient. Even if the drug elimination half-life were to double (to 5 hours), sufficient time will elapse during a 24-hour dosing interval to allow drug concentrations to reach the targeted 1 μg/mL. Note that the trough sample was not collected in this patient just before the next dose (i.e., at 24 hours). The drug would not have been detectable at that time; hence trough concentrations were collected after two predicted drug half-lives had elapsed.		

seizures in a dog with subtherapeutic concentrations is not justification for discontinuing the drug. On the other hand, some animals may respond only if concentrations are higher than the recommended maximum concentration. Drug concentrations need not necessarily be reduced if there is no concern regarding toxicity or in the absence of side effects, even if the maximum therapeutic range has been surpassed (e.g., bromide).

Dose Modification with Kinetic Calculations

Most dose modifications do not require kinetic calculations (see next section). If elimination half-life, a proper dosing interval, or a dose based on changes in patient Vd is necessary, then kinetics can be determined. The minimum number of data points needed to develop a pharmacokinetic profile in a patient is two. Generally for TDM, these two samples consist of the peak and trough (see Fig. 4–1*A*) collected during a single dosing interval at steady state. Alternatively, for the sake of convenience, a trough sample can be collected just before a dose and the peak sample collected 2 to 5 hours (when appropriate for the drug) dosing. This protocol assumes that the drug is handled the same way by the body during each dosing regimen and that the dose is the same. Although this is true, conditions such as diurnal variation and treatment can alter drug disposition between dosing intervals. Often, the dose is not the same for both morning and evening.

Regardless of when the samples are collected (assuming that they are collected after absorption and distribution are complete), when the points are plotted on semilogarithmic paper, the slope between the two points reflects k_{el} (see Fig. 4–1*A*), which is used to determine drug half-life in the patient (see Chapter 1). Half-life can be either calculated or estimated from the PDC versus time curve drawn on semilogarithmic paper. The two points are connected, and the resultant line is extrapolated to both the x and y axes. For estimation, the time that must elapse between any two concentrations on the line where one concentration is twice the second is the half-life (Figure 4–1*A*). The half-life also can be calculated from k_{el} (the slope, or rise $[C_1 - C_2]$ over the run $[t_2 - t_1]$). The line does not need to be plotted to calculate elimination half-life, but the time that each dose was given and each sample was drawn must be known for the calculations (see Figs. 4–1 and 4–2). Half-life can be used to determine the maximum time that can elapse between doses in the patient before PDCs do not fall below the recommended minimum effective concentration during the dosing interval (T_{max}) (see Figs. 4–1*A* and 4–2).

The Vd of drugs administered IV can be calculated from the peak PDC and dose (see Fig. 4–2 and Case 6). If the drug is 100% bioavailable after oral, subcutaneous, or intramuscular administration, Vd can also be estimated from these data. For orally administered drugs for which the bioavailability is not known, a population Vd measured in normal animals must be used. The individual patient Vd may not, however, be accurately estimated by population Vd. Changes in patient Vd compared with those in normal animals can be somewhat accommodated if information regarding patient factors that influence Vd, such as obesity, edema, ascites, dehydration, and serum protein concentrations, are known (see Chapters 1 and 2).

The Vd is used to calculate the amount of drug that must be administered to achieve C_{max}, the target (generally maximum) effective drug concentration (loading dose $[D_L]$), and the amount of drug necessary to replace drug eliminated during the dosing interval (maintenance dose, D_{max}) (see Fig. 4–2). Once D_{max} and T_{max} have been established, dosing regimens can be appropriately altered to ensure that PDCs fall within a recommended therapeutic range (see Fig. 4–2). In addition to calculation of patient pharmacokinetic parameters, another advantage to collecting both a peak and a trough drug sample is that the achievement of a minimum effective concentration (C_{min}) and avoidance concentrations above the maximum (C_{max}) throughout the dosing interval can be confirmed.

Dose Modification Without Kinetics

Not all modifications in dosing regimens require pharmacokinetic calculations. If a patient has drug concentrations outside the therapeutic range, the response is obvious; dose should be modified to bring the drug concentrations into the therapeutic range. Generally, a dose can be modified using one of the following equations, as long as concentrations were measured at steady state:

$$\text{New dose} = \text{Old dose} \times \frac{\text{Targeted PDC}}{\text{Observed patient PDC}}$$

or

$$\text{New interval} = \text{Old interval} \times \frac{\text{Observed PDC}}{\text{Targeted PDC}}$$

Modifications of dosing regimens for patients whose drug concentrations are inside the therapeutic range are more problematic. The next step becomes more obvious, however, when one remembers that the data reflect the individual patient, whereas a range was established for a sample population. A range reflects the concentrations between which most (95%) of the patients are expected to respond. For the individual patient, however, where in the range that patient should be may not be obvious. Some patients will respond at the low end of the range, some will not respond until the maximum is reached, and a smaller percentage of the population will respond at concentrations outside the recommended range. Therapeutic drug monitoring identifies the therapeutic range in the patient.

If a patient has not responded, even though "in" the therapeutic range, we stair step drug concentrations gradually until either the patient responds or the maximum end of the range is reached and the risk of adverse effects becomes too great. We take the same approach, but in the reverse direction, if drug concentrations are too high and we want to decrease drug concentrations to a minimum effective dose. The decision as to whether to change the dose or the interval depends on the drug itself, its therapeutic index, and the need to maintain PDCs within the therapeutic range throughout a dosing interval.

Even if TDM is used to ensure that the PDC stays within a therapeutic range during a dosing interval, a patient may react adversely (including failure to respond therapeutically). Disease, age, and other factors may play a role in the minimum or maximum effective concentration appropriate for each patient (see Cases 2, 5 and 6). Therefore, it is imperative that PDCs be interpreted in conjunction with the desired therapeutic end point (i.e., complete eradication of seizures vs. a decrease in the severity and frequency) as well as the clinical status of the patient. This is particularly important for tests for which there is great overlap between "normal" and "abnormal" ranges (e.g., digoxin, thyroid hormones). Many practitioners have available to them instrumentation necessary to monitor phenobarbital and thyroid function.

WHERE THERAPEUTIC DRUG MONITORING IS OFFERED

Currently, TDM is being offered as an aid to rational drug therapy at several veterinary academic institutions and veterinary diagnostic laboratories throughout North America (Neff-Davis, 1988). The availability of TDM for specific drugs varies with the laboratory. In addition, TDM has received wide acceptance in the human medical field (Goldstein, 1989), and clinical laboratories providing TDM services to human patients may also be amenable to provision of the same services to veterinary practitioners. Note, however, that costs of testing in human patients often far exceeds what pet owners are willing to pay for the same testing in their animal.

In human laboratories used to determine drug concentrations in animals, therapeutic ranges (e.g., for clorazepate and bromide) can differ between animals and people. Regardless of the type of laboratory, veterinarians should choose laboratories that follow a good quality assurance program. This means that assays that detect drugs have been validated in the species of interest and that controls are used daily or with each test to ensure that the assay is valid. Many veterinary laboratories use automated assays

Table 4–2. Effects of Drugs and Other Artifacts on Therapeutic Drug Monitoring Results

Drug	Artifact	Sequelae
All drugs	Serum separator tubes	Silicone gel can bind drug, decreasing concentrations
Aminoglycosides	1. Glass tubes 2. β-Lactams	1. Glass binds drug, decreasing concentrations 2. High concentrations of β-lactam antibiotics inactivate aminoglycosides, decreasing concentrations
Bromide	Increased serum chloride	Depending on assay, chloride cannot be distinguished from bromide, resulting in artifactually high chloride concentrations
Digitalis glycosides	Red stoppers	Stopper may bind drug, decreasing concentrations
Phenobarbital, phenytoin, primidone	Drugs	Concentrations are decreased by phenobarbital-induced drug metabolism and other drugs that stimulate drug metabolism; concentrations are increased by cimetidine, chloramphenicol, and other inhibitors of drug metabolism; concentrations are increased by clorazepate if concentrations are high
Thyroid hormones	Drugs	Phenobarbital increases peripheral metabolism and may decrease concentrations
Theophylline	Drugs	Concentrations are increased by drugs that decrease metabolism, including enrofloxacin, imidazole antifungals, and cimetidine

that were designed to measure drugs in humans. To assume that the assays will detect the drug in animals is incorrect.

Constituents in plasma differ substantially between species, and these constituents can interfere with the methodology of some assays. Bromide analysis offers a unique concern. The assay (gold chloride method) to accurately detect bromide in serum is tedious, and many laboratories do not offer it because it is time consuming. Some laboratories use a bromide-sensitive ion probe, which is very easy and can be rapidly performed. Unfortunately, the probes are not able to distinguish high concentrations of bromide (above 1.5 mg/mL) from other ions present at high concentrations in the serum (such as chloride), and manufacturers of the probe may state that the probe should not be used to measure bromide in serum. Because of the inability to accurately detect all concentrations in the therapeutic range, laboratories that use this technique may limit normal values to concentrations that can be accurately detected rather than to an actual therapeutic range. Laboratories chosen for monitoring should be contacted before use to ensure that quality control procedures are followed and that assays used in animals have been validated.

Attention should be given to how the sample collected from the patient is handled. Some drugs require refrigeration or freezing (Table 4–2). Sample size may vary for each drug or even for the same drug depending on the method the laboratory uses. Drugs can interact with the containers in which they are collected or mailed. In general, serum separator tubes should not be used to collect or mail samples containing drug. Drugs can bind to the silicon gel, which decreases concentrations measured in blood. Aminoglycosides can bind to glass; samples should be collected and submitted in plastic tubes. The effects of hemolysis and hyperlipidemia on drug assays vary. In general, it is wise to avoid either in sample collection. Although sample handling is often the same for each drug, the laboratory to which the sample will be submitted should be contacted before the sample is sent for TDM analysis. Idiosyncrasies regarding timing of sample, collection, and storage apparatus (i.e., tubes and anticoagulants), mailing instructions (including conditions), and cost should be known before collection.

In summary, TDM can aid clinicians in the titration of drug doses to the individual patient, thus avoiding adverse reactions that are a direct consequence of patient variability in drug disposition. In addition, TDM ensures that optimal drug concentrations are established promptly and that therapeutic drug concentrations are maintained, thus avoiding a protracted period of ineffective drug therapy.

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SECTION TWO

A Therapeutics Approach

5

Fluids, Electrolytes, and Acid-Base Therapy

Michael D. Willard

- PHYSIOLOGY
- Water
- Sodium
- Potassium
- Acid-Base Status
- DISEASE-INDUCED CHANGES
- Sodium
  - Hypernatremia
  - Hyponatremia
- Chloride
  - Hypochloremia
  - Hyperchloremia
- Potassium
  - Hyperkalemia
  - Hypokalemia
- Miscellaneous Minerals
- Acid-Base Status
  - Metabolic Acidosis
  - Metabolic Alkalosis
  - Respiratory Alkalosis
  - Respiratory Acidosis
  - Blood Gas Analysis
- FLUIDS
- Calculation
  - Maintenance Fluid Needs
  - Deficit Fluid Needs
  - Ongoing Losses
- Choice of Fluid
- Route of Administration
- Determining Adequacy or Inadequacy of Fluid Therapy
- ELECTROLYTES
- Considerations for Therapy
- Hyponatremia
- Hypernatremia
- Hypochloremia
- Hyperchloremia
- Hypokalemia
- Hyperkalemia
- Hypophosphatemia
- Hypomagnesemia
- ACID-BASE STATUS
- Considerations for Therapy
  - Metabolic Acidosis
  - Metabolic Alkalosis
  - Respiratory Acidosis and Alkalosis
- Drugs Used to Correct Acid-Base Abnormalities
- SPECIAL CONSIDERATIONS
- Shock
  - Hypovolemic Shock
  - Obstructive Shock
  - Cardiogenic Shock
  - Distributive Shock
- Renal Disease
  - Polyuric Renal Failure
- Oliguric and Anuric Renal Failure
  - Urethral Obstruction
  - Nephrotic Syndrome
- Heat Stroke
- Cardiac Disease
- Gastrointestinal Disorders
  - Acute Vomiting
  - Chronic Vomiting
  - Acute Diarrhea
  - Chronic Diarrhea
- Pancreatic Disease
  - Acute Pancreatitis
  - Diabetic Ketoacidosis
- Hepatic Disease
- Hypoglycemia
- Hypocalcemia
- Hypercalcemia
- SURGERY

PHYSIOLOGY

Water

Approximately 60% of a normal animal's body weight is composed of water, with variation between and within species. This percentage is affected by fat and age; obese and older animals tend to have a small percentage of body weight composed of water. Of this 60%, slightly over half (approximately 33%) is within the body's cells and is referred to as the *intracellular fluid compartment* (ICF). The remaining 27% is outside (i.e., between) the cells and is referred to as the *extracellular fluid compartment* (ECF). The ECF may be further divided into subcompartments (i.e., plasma, 5%; interstitial fluid, 8%; transcellular fluid, 2%; dense connective tissue and bone, 12%) (Rose, 1984a; Edelman and Leibman, 1959).

Under normal, steady-state conditions, water is freely diffusible throughout the body because all compartments have the same osmolality (approximately 290 to 310 mOsm/kg in dogs and 300 to 330 mOsm/kg in cats [Hardy and Osborne, 1979]). The osmolality of a fluid can be measured by freezing point depression or vapor pressure osmometry. Alternatively, serum (i.e., ECF) osmolality can be approximated by many formulas (i.e., $\text{mOsm/kg} = 2[\text{Na} + \text{K}] + [\text{serum glucose in mg/dL} \div 18] + [\text{BUN in mg/dL} \div 2.8]$, where BUN is blood urea nitrogen). The accuracy of this formula depends on the absence of unusual particles (e.g., ethylene glycol) that are not expected to be found in serum.

As can be seen from the above formula, sodium is principally responsible for ECF osmolality. Osmolality in the ICF is principally determined by potassium, magnesium, phosphates, and proteins. To cause water to move from one compartment to another, one must change the tonicity of one or more compartments (Guyton, 1986). Tonicity (which is sometimes considered "effective" osmolality) refers to particles that cannot readily diffuse across membranes. Because such particles cannot readily diffuse across a membrane, it is possible for there to be greater or lesser concentrations of particles on one side, depending on body transport mechanisms. An accumulation of such particles on one side of a semipermeable membrane can cause the osmolality on that side of the membrane to be greater than what is found on the other side of the membrane. When the osmolality on one side of a membrane is greater than on the other side, either particles or water will diffuse from one side to the other until there is isotonicity (i.e., the same osmolality on both sides of the membrane). If the particles cannot diffuse, then the water must. Thus, by increasing or decreasing on one side of the membrane the number of these particles that cannot readily diffuse across the membrane, water can be made to enter or leave that compartment. In such conditions, we say that these particles are "effective" in exerting oncotic pressure and causing fluid to move. This is in contrast to particles that freely diffuse across cell membranes (e.g., BUN).

If there are too many or too few diffusible particles on one side of a membrane, they, rather than water, will passively diffuse across the membrane until the quantities of particles are equal on both sides. Thus, particles that freely diffuse across membranes contribute to osmolality but do not exert tonic pressure. Extracellular fluid sodium is a good example of a particle that is responsible for tonicity. Even though it can diffuse across cellular membranes, Na-K ATPase that is present in most cellular membranes (except for most canine and feline red blood cell membranes) maintains a very low intracellular sodium concentration. Hence, if sodium is added to the ECF, it stays there and increases the osmolality and tonicity. Consequently, water is be drawn out of the ICF and into the ECF compartments until the osmolalities of the two fluid compartments are nearly equal. Chloride atoms usually follow sodium atoms in order to maintain electroneutrality; hence, whenever a sodium atom moves, it usually means that there are two particles that have been added or subtracted from a compartment: sodium and chloride. Glucose is another particle that has a major contribution to plasma tonicity. Although it can enter the cell, it does not do so rapidly in the absence of insulin (Rose, 1984a).

Albumin is not important for distribution of water between the ICF and ECF; however, it is important for distribution of water within the ECF. Albumin contributes most to tonicity at the level of the capillary. In the capillaries, sodium and glucose can pass freely into the lymph while albumin is retained in the vessel, where it exerts a tonic force, drawing fluid back into the capillary (Rose, 1984a).

The total amount of water in the body is determined by intake versus loss (Rose, 1984a). There are obligatory water losses into the urine, feces, and expired air of all animals. There can also be excretion of free water into urine. Occasionally, there may be significant obligatory cutaneous losses, but this is uncommon in dogs and cats. Obligatory water losses in dogs include panting, and subsequent loss of fluid in saliva can be important in that species. Obligatory urinary and fecal losses are determined by the solute load that must be excreted. Respiratory losses of water are affected by ambient temperature and humidity. Water loss may increase due to symptoms such as vomiting, diarrhea, and polyuria. Fever can also be responsible for increasing loss of water from a patient (Rose, 1984b).

Urinary free water loss refers to water excreted above and beyond that needed to eliminate renal solute. This water is excreted due to modification of antidiuretic hormone (ADH) secretion. Antidiuretic hormone is normally released from the posterior pituitary gland when osmoreceptors in the hypothalamus detect hypertonicity and when baroreceptors in the cardiovascular system sense hypovolemia. Release of ADH causes water to be retained in the body. For free water to be excreted by the kidneys, there must be suppression of ADH release, adequate delivery of tubular fluid to a properly functioning ascending limb of the loop of Henle, and the renal collecting ducts must function normally (i.e., they must be impermeable in the absence of ADH) (Sterns and Spital, 1990).

Water intake occurs principally by drinking, although food consumption may also contribute significantly, depending on the food. Not only may different foods contain different percentages of water, but metabolism of nutrients also produces what is referred to as "metabolic water" (Anderson, 1983). Thirst is controlled by the central nervous system and is rarely defective unless there is neurologic disease or a congenital abnormality of that area of the brain.

Sodium

Sodium intake normally occurs when an animal eats or drinks (Briggs et al., 1990). Animals receiving medications may, however, have substantial sodium intake via drugs. Under normal circumstances, the kidneys regulate sodium loss from the body, excreting as much sodium as is ingested. The renal excretion of sodium is regulated by aldosterone, atrial natriuretic factors, and intrinsic renal mechanisms (i.e., glomerulotubular balance and renal hemodynamic factors). Glomerulotubular balance refers to the ability of the kidney to maintain a relatively constant fractional reabsorption of sodium, despite changes in the glomerular filtration rate.

If there is expansion of the effective circulating volume (i.e., overhydration or excessive water in the ECF), the cardiac atria will be distended and release atrial natriuretic factors. These factors inhibit the production and the effects of angiotensin as well as decrease reabsorption of sodium from the renal medullary collecting ducts. Hypoperfusion of the kidneys or decreased delivery of sodium to the macula densa activates the renin-angiotensin system, causing more sodium to be reabsorbed from the renal tubules. Aldosterone also is released from the adrenal cortex, increasing sodium reabsorption from the renal cortical collecting ducts (DiBartola, 1992a).

Potassium

Regulation of total body potassium and plasma potassium concentration is important because potassium has a major influence on resting cellular membrane potentials (DiBartola and Autran de Morais, 1992). Hypokalemia lowers the resting membrane potential, making it more difficult to achieve an action potential and subsequent contraction of a muscle. Hyperkalemia raises the resting membrane potential, which may result in a diminished action potential amplitude or, in extreme cases, continuous depolarization of the cell membrane. Most of the body's potassium is found within cells, yet the plasma concentration has significant effects on body function. Potassium regulation thus is more complicated than sodium regulation.

Potassium homeostasis is best conceptualized as being divided into internal and external balance. External balance refers to the total amount of potassium in the body and is determined by intake versus loss. Potassium enters the body principally via food, and almost all ingested potassium is absorbed. Relatively little potassium is normally excreted in the feces, although this can become an important route in disease. Normal potassium loss occurs predominantly via the kidneys, depending on ECF potassium concentration and secretion of aldosterone. Although this is a very effective means of eliminating potassium from the body, this mechanism cannot adjust rapidly enough to maintain normal plasma potassium concentrations when larger than normal amounts of potassium are ingested (Rose, 1984c).

Internal potassium balance refers to the distribution of potassium into the ICF and ECF compartments. The Na-K ATPase found in cellular membranes actively transports potassium into the cell and maintains a high intracellular concentration (i.e., approximately 150 mEq/L). Additional potassium may, however, need to be sequestered in the cells until the kidneys have time to eliminate it (as in the case of an animal suddenly eating a meal containing several times as much potassium as it is used to eating). In such cases, insulin and epinephrine augment the transport of potassium into the cells, safely storing additional potassium until it can be eliminated (Rose, 1984c). The internal balance mechanisms should be thought of as a temporary measure designed to allow the kidneys and colon time to complete their job (Willard, 1989; DiBartola and Autran de Morais, 1992).

Acid-Base Status

The body must deal with very large amounts of acid (H^+) that are generated daily. This is important because H^+ is very reactive, and small amounts (i.e., nanoequivalents) have detrimental effects on proteins (i.e., enzymes, cell membranes). For example, a pH of 7.40 is a normal blood pH. If the pH falls to 7.20 (which is an increase of approximately 20 nEq H^+/L), the patient may have decreased cardiac output and be predisposed to arrhythmias (DiBartola, 1992b; Rose, 1984d).

One may view acid-base physiology as having an external and internal balance, much as occurs for potassium. External balance consists of eliminating acid from the body, while internal balance consists of safely sequestering excessive acid until it can be excreted. There are, however, two categories of acid found in the body: nonvolatile (produced by metabolism, especially of proteins and ammonium, in the liver) and volatile; CO_2 produced by cellular respiration throughout the body (DiBartola, 1992b), each being handled differently.

Nonvolatile (also called *fixed*) acid (H^+) is primarily excreted by the kidneys, whereas volatile acid is eliminated via the lungs as CO_2. Sequestration of acid is called *buffering* and involves reacting the H^+ with something (i.e., a buffer) that can combine with it and yet result in a minimal change in pH, generating usually a weak acid plus its conjugate salt. There are many buffers throughout the body. The principle buffer in the ECF is the bicarbonate-carbonic acid system, which only reacts with nonvolatile acid. Calcium carbonate and calcium phosphate in bone have a major buffering capacity, whereas intracellular phosphates and proteins are important for both volatile and nonvolatile acids. Volatile acid (CO_2) is not buffered by the bicarbonate system; it is buffered by proteins, especially the hemoglobin in red blood cells (DiBartola, 1992b; Rose, 1984d).

The pH of the ECF is ultimately determined by how effectively these buffering and elimination mechanisms work. Understanding the effects of the different types of acids and buffers on pH may be aided by considering the Henderson-Hasselbalch equation. This equation is not completely accurate, and another system (i.e., strong ion difference [SID]) avoids some of the oversimplifications in the Henderson-Hasselbalch formula (Autran de Morais, 1992a). The SID system recognizes a distinction between independent variables (i.e., P_{CO_2} and SID), total nonvolatile weak acids (i.e., $[A_{tot}]$, which are primarily composed of plasma proteins), and dependent variables (i.e., $[HCO_3^-]$ and $[H^+]$). This allows one to understand changes in $[HCO_3^-]$ in terms of alterations in SID, P_{CO_2}, and $[A_{tot}]$. The clinical value of the SID system over the traditional Henderson-Hasselbalch formula is currently uncertain. For that reason, and because the latter equation is easier for the beginner to conceptualize and yet allows one to sufficiently understand the processes involved to diagnose and treat most clinically significant acid-base disorders, the Henderson-Hasselbalch equation is considered in this discussion. That equation is

$$pH = 6.1 + \log([HCO_3^-] \div 0.03 \times P_{CO_2})$$

Clinically, the most important aspect of this formula is that it is the ratio of the blood bicarbonate concentration to the partial pressure of CO_2 that determines the ECF pH, not just the concentrations (Rose, 1984d).

The blood bicarbonate concentration is normally maintained by the kidneys. The kidneys reabsorb filtered bicarbonate and regenerate bicarbonate that has buffered (i.e., "titrated") acid. In this way, bicarbonate may be thought of as a "conveyer belt." It combines with nonvolatile acid (i.e., H^+), which protects the pH. It then takes the acid to the kidney where the H^+ is excreted, and the bicarbonate is regenerated so that it can go back and do the same thing. When the bicarbonate has titrated an H^+ atom, it is no longer bicarbonate, and hence the concentration of bicarbonate decreases until the bicarbonate regenerates. If there is so much acid that the bicarbonate system cannot buffer it quickly enough, the additional acid is buffered by other systems, especially intracellular protein and phosphate (Rose, 1984e).

When there is excessive nonvolatile acid present, it reacts with the bicarbonate buffer systems (and others, depending on the magnitude of the increase). The plasma bicarbonate concentration decreases as the bicarbonate combines with H^+ and forms H_2CO_3. The result is that the HCO_3^-:P_{CO_2} ratio decreases, meaning that the pH is less and there is acidemia (i.e., too much acid in the blood). We would say that this patient had a "metabolic" acidosis because it has a disorder causing excessive nonvolatile acid. The body will try to re-establish the ratio (and thereby the pH) by lowering the $\mathrm{P_{CO_2}}$ by hyperventilation. This is a normal compensatory response. If the underlying disorder persists, the pH will not become normal, but will be closer to normal than it was before the compensatory response. Although less common, excessive loss of $\mathrm{HCO_3^-}$ from the body (as might occur with some types of diarrhea) could result in the same ratio and the same compensatory response (Rose, 1984f).

When there is excessive volatile acid present, it does not react with the plasma bicarbonate. The $\mathrm{P_{CO_2}}$ of the plasma will be increased, which increases the denominator of the $\mathrm{HCO_3^-:P_{CO_2}}$ ratio, thus decreasing the ratio and resulting in a lowered pH: an acidemia. This patient would be said to have a "respiratory" acidosis because it has a pulmonary dysfunction that is resulting in the increased $\mathrm{P_{CO_2}}$. The normal compensatory response by the body would be to increase the numerator (i.e., increase serum bicarbonate concentration by decreasing renal excretion) (Rose, 1984f).

When there is an excess of plasma bicarbonate, the ratio increases, and the resulting high pH (i.e., alkalemia) is due to a metabolic alkalosis. The normal compensatory response is to have the lungs excrete less CO_2. Finally, if there is a deficiency of CO_2 (due to hyperventilation), the ratio increases, and the animal has a respiratory alkalosis. The normal compensatory response is to excrete additional bicarbonate into the urine until the normal ratio is re-established (Rose, 1984g).

Compensation normally occurs quickly. In dogs, one may anticipate the approximate degree of a compensatory response if the body is functioning normally; cats are not as predictable. A general rule is that the body never overcompensates for an acid-base disorder and, with the possible exception of chronic respiratory alkalosis, is not efficient enough to return the pH all the way back to the normal range (DiBartola, 1992b).

DISEASE-INDUCED CHANGES

Sodium

Changes in plasma sodium concentration usually reflect changes in total body water content. Hyponatremia and hypernatremia primarily cause clinical problems by overhydrating or dehydrating the brain (ICF). However, the severity of clinical signs may correlate more closely with the rapidity of change rather than with the degree of hyponatremia or hypernatremia. If the serum sodium concentration changes slowly, the brain can usually adjust the number of osmotically active particles in its cells and protect itself. Thus, prevention is preferred to treatment, and treatment should be gradual rather than sudden (Rossi and Schrier, 1987).

Hypernatremia

Hypernatremia may be due to either addition of sodium to the body or loss of free water without replacement (DiBartola, 1992a; Hardy, 1989). The latter is probably the most common cause in dogs and cats. The thirst mechanism is so effective that it is exceedingly rare that hypernatremia occurs in animals that have access to adequate volumes of water and can drink. Hypernatremia should cause one to consider the diagnoses listed in Table 5–1.

Table 5–1. Causes of Hypernatremia

- Normal loss of free water with inadequate replacement
  - Failure to provide water to an animal that can drink
  - Inadequate fluid therapy for an animal that cannot drink
    - Unconscious animal
    - Animal that is not being fed or watered per os
    - Animal with an oral, pharyngeal, or esophageal disease that prevents ingestion
    - Adipsia
- Excessive loss of free water with inadequate replacement
  - Diabetes insipidus
  - Heat stroke
  - Fever, hyperthermia
  - Hypotonic fluid losses
    - Diarrhea
    - Vomiting
    - Polyuria
- Excessive intake of sodium
  - Salt poisoning
  - Administration of sodium
    - Hypertonic saline
    - Sodium bicarbonate

Hyponatremia

Hyponatremia can be due to addition or retention of water in excess of sodium to the body or the ECF or to loss of sodium from the body. Hyponatremia may be caused by several mechanisms, and a systematic approach to determining the cause is necessary. Evaluation of plasma osmolality is the first step (Table 5–2) (DiBartola, 1992a). Hyponatremia with concurrent normal plasma osmolality suggests a laboratory artifact. Hyponatremia with concurrent plasma hyperosmolality suggests that there are other osmotically active particles in the plasma (i.e., glucose, mannitol) that are drawing water out of the ICF and into the plasma, thus diluting the sodium that is present (DiBartola, 1989, 1992a).

Table 5–2. Evaluation of the Patient with Hyponatremia

- Normo-osmolal patients
  - Look for artifact (i.e., pseudohyponatremia due to hyperlipidemia or hyperproteinemia)
- Hypo-osmolal patients
  - Hypovolemic patients
    - Gastrointestinal loss of hypotonic fluid with water replacement
    - Hypoadrenocorticism
    - Salt-losing nephropathies
    - Sequestration of fluids or sodium in third spaces
  - Hypervolemic patients
    - Congestive heart failure
    - Nephrotic syndrome
    - Hepatic disease (especially cirrhosis)
  - Normovolemic patients
    - Primary polydipsia
    - Administration of hypotonic fluids
- Hyperosmolal patients
  - Hyperglycemia
  - Mannitol infusion

Patients with hyponatremia and concurrent plasma hypo-osmolality should next be determined to be either hypovolemic, normovolemic, or hypervolemic. Hyponatremia in a hypo-osmolal, hypervolemic patient is often due to congestive heart failure, nephrotic syndrome, or severe hepatic disease (usually cirrhosis). Each of these diseases may cause so much retention of water that even though the animal's total body sodium is increased, the patient still becomes hyponatremic. These disorders tend to cause poor perfusion despite adequate blood volume (i.e., decreased "effective" circulating volume). Therefore, the body retains fluid in an effort to expand the circulating volume, something that normally improves peripheral perfusion if the patient is dehydrated but does not help these animals. Poor renal perfusion can also result in decreased delivery of fluid to distal diluting sites in the tubules with subsequent fluid retention. There are additional mechanisms proposed for each of these disorders (DiBartola, 1992a).

Hyponatremia in a hypo-osmolal animal that is hypovolemic suggests either hypotonic fluid loss with subsequent replacement of the water only, third space losses, or loss of sodium from the body. Note that loss of hypotonic fluids (i.e., fluids in which there are relatively small amounts of sodium) via vomiting, diarrhea, or polyuria can cause either hypernatremia or hyponatremia. If the water loss is not replaced, the animal will be hypernatremic and dehydrated because, despite losing both water and sodium, it has lost more water than sodium. If the patient drinks water however (i.e., replaces the hypotonic fluid loss with water that has even less sodium), hyponatremia will result. The patient may still be hypovolemic for two reasons. First, there may be ongoing losses. Second, and more importantly, loss of hypotonic fluid from the ECF means that there is less tonic pressure holding water in the ECF (due to the loss of sodium). When the patient drinks water, relatively more of it goes into the ICF (which has not lost its osmotically active particles) so that, even if the patient has adequate total body water, maldistribution results in a deficient ECF (DiBartola, 1989, 1992a).

Sodium may be lost from the body due to hypoadrenocorticism and other salt-losing nephropathies (e.g., pyelonephritis, diuretic administration). These patients may be distinguished from those with gastrointestinal losses of hypotonic fluids by examining the urinary sodium concentration. Under normal circumstances, a hypovolemic patient with hyponatremia seeks to prevent renal sodium losses as a means of restoring ECF. Consequently, there will be very little sodium in the urine. Animals in which renal losses are the cause of the hyponatremia will, however, have substantial urinary sodium concentrations (DiBartola, 1989).

Hyponatremia in a normovolemic, hypo-osmolal patient is uncommon in dogs and cats. Primary polydipsia (also called *psychogenic polydipsia*) and overzealous administration of hypotonic fluids are the most common causes (DiBartola, 1992a).

Chloride

Changes in plasma chloride concentration are important from the standpoint of the effects they have on acid-base status. In particular, hypochloremia is closely associated with metabolic alkalosis (DiBartola, 1992c). Hyperchloremia tends to be associated with acidosis.

Hypochloremia

The major causes of hypochloremia are increased losses due to vomiting of gastric contents or excessive administration of loop diuretics (e.g., furosemide) (DiBartola et al., 1994). Chloride losses due to gastric vomiting are usually associated with hypokalemia and metabolic alkalosis. Occasionally, a paradoxical aciduria is also seen. History, physical examination, and these other laboratory findings are usually diagnostic of vomiting. A history of aggressive furosemide administration, especially in an anorexic animal, is also usually sufficient for diagnosis. Rarely, administration of large doses of sodium without administration of chloride (e.g., high doses of sodium penicillin G) may cause hypochloremia. When a hypochloremic patient is also hyponatremic, hyperkalemic, or both, one should consider hypoadrenocorticism. If, however, one corrects the plasma chloride concentration for the plasma water, i.e.,

$$\text{Dogs: Corrected Cl}^- = \text{plasma Cl in mEq/L} \times (146 \div \text{plasma Na in mEq/L})$$

$$\text{Cats: Corrected Cl}^- = \text{plasma Cl in mEq/L} \times (156 \div \text{plasma Na in mEq/L})$$

one will find that patients with hypoadrenocorticism may have a normal or increased corrected chloride level (DiBartola et al., 1994). There seldom seems to be a major diagnostic or therapeutic benefit to determining the corrected plasma chloride concentration.

Hyperchloremia

Hyperchloremia is principally found in animals that are hypernatremic due to loss of free water and in those that have received fluids containing proportionally more chloride than sodium relative to plasma values. Examples of the latter include physiologic saline solution (PSS), Ringer's solution, and especially PSS supplemented with potassium chloride. Hyperchloremia may also be present in animals that have a metabolic acidosis associated with a normal anion gap (i.e., hyperchloremic metabolic acidosis). This acid-base change may be seen in some animals with excessive bicarbonate loss due to severe diarrhea (DiBartola et al., 1994).

Potassium

Changes in the plasma potassium concentration are important because of their effects on cellular metabolism and especially on the resting membrane potentials and the subsequent strength of contraction when an action potential is generated (Rose, 1984c). Hypokalemia and hyperkalemia both cause muscular weakness. Hypokalemia also predisposes the heart to arrhythmias and makes it difficult to control arrhythmias pharmacologically. Plasma potassium concentrations of 8.0 mEq/L or higher and of 2.0 mEq/L or lower are potentially life threatening, although lesser changes can be dangerous if there are other, augmenting changes (e.g., hyponatremia, hypocalcemia, or hypercalcemia) (Willard, 1989).

Hyperkalemia

Hyperkalemia may be artifactual or real. If it is real, it is either iatrogenic (increased intake or other drug reaction) or spontaneous. The major cause of spontaneous hyperkalemia is decreased urinary excretion due to either renal or adrenal disease (Table 5–3) (Willard, 1989).

White blood cells (WBCs) and platelets contain potassium that can be released when blood clots and excessive numbers of these cells lyse. This is usually only a problem if there are more than 100,000 WBC/µl (e.g., leukemic patients) or more than 800,000 platelets/µl (Bellevue et al., 1975; Reimann et al., 1989). Red cell lysis does not cause a problem unless the particular animal that is being sampled has red blood cells with a high intracellular potassium content. This is most common in Akitas but may occur as a genetic trait in almost any dog (although it is rare) (Degen, 1987). If there is any doubt as to whether the hyperkalemia is artifactual or real (i.e., finding hyperkalemia in an animal that one would not expect to find it in), one should obtain a lithium heparin-anticoagulated blood sample and promptly harvest the plasma before any of these cells lyse. Such a sample should be used routinely as it will prevent pseudohyperkalemia from any of these causes (DiBartola et al., 1994).

The list of drugs that may cause hyperkalemia is impressive (Willard, 1989). With the exception of excessive administration of potassium chloride in intravenous fluids, however, significant hyperkalemia due to drug administration is rare and usually only occurs if there is underlying renal or adrenal dysfunction. Only the more common causes are provided in Table 5–3.

Decreased urinary potassium excretion may be due to severe primary renal dysfunction (e.g., typically anuric or oliguric renal failure) or to secondary renal dysfunction due to aldosterone deficiency (i.e., hypoadrenocorticism). Third space disorders (e.g., fluid accumulations in the pleural or peritoneal cavities) (Willard et al., 1991) and some gastrointestinal diseases (i.e., whipworms) (Graves et al., 1994) rarely cause hyperkalemia through uncertain mechanisms. One should identify hypoadrenocorticism early as it has an excellent prognosis if treated correctly; an adrenocorticotropic hormone-stimulation test is required for definitive diagnosis.

Table 5–3. Causes of Hyperkalemia

- Artifactual
  - Pseudohyperkalemia
  - Lysis of red blood cells that have high potassium concentrations (generally only seen in selected breeds and families)
  - Thrombocytosis
  - Extreme leukocytosis
- Iatrogenic
  - Administration of potassium chloride or other potassium-containing drug
  - Potassium-sparing diuretics
  - Trimethoprim-sulfa
  - Propranolol
  - Angiotensin-converting enzyme inhibitors (e.g., enalapril)
  - Heparin
  - Massive digitalis overdose
- Decreased excretion
  - Acute renal failure (especially anuric or oliguric)
  - Hypoadrenocorticism
  - Third space disorders
  - Miscellaneous
    - Gastrointestinal (e.g., whipworms)

Renal failure should usually be considered next. If third space disorders (especially chylothorax or ascites) or whipworms are present, one may have to eliminate them and see if the hyperkalemia returns. Most patients with hyperkalemia due to renal failure have acute failure with oliguria or anuria. Not all acute renal failure patients have hyperkalemia, however, and not all hyperkalemic, oliguric patients have acute disease. Furthermore, some patients appear to have damage to the renal tubules at the site of the action of aldosterone and have hyperkalemia despite relatively moderate increases in serum creatinine and no evidence of oliguria. One must eliminate other causes of hyperkalemia in such patients; diagnosis of renal hyperkalemia is made by exclusion (Willard, 1989; DiBartola and Autran de Morais, 1992).

Hypokalemia

Hypokalemia may be caused by decreased intake, increased loss, intracellular sequestration of potassium, or a combination thereof. Decreased intake, while contributing to hypokalemia due to other causes, is rarely sufficient by itself to cause clinically significant hypokalemia. Sequestration of potassium is usually iatrogenic and caused by insulin administration, although an acute, severe alkalemia may be responsible (Rose, 1984c).

Increased loss of potassium is the most important cause of hypokalemia in dogs and cats. Gastrointestinal losses due to vomiting and diarrhea are the most common, although renal losses may be due to drugs (e.g., furosemide) or spontaneous renal disease. The latter is relatively common in older cats and often is not associated with azotemia. If in doubt as to the cause, one may calculate the fractional excretion of potassium (FE_K) into the urine. Animals that are hypokalemic due to nonrenal causes should have normal (approximately 4% to 6%) to decreased FE_K, whereas cats with potassium-losing nephropathies usually have values more than 6% to 10% (Dow et al., 1987a, b; DiBartola and Autran de Morais, 1992).

Miscellaneous Minerals

Miscellaneous minerals that occasionally concern the clinician are phosphorus and magnesium. Severe hypophosphatemia is principally seen in diabetic ketoacidotic patients that are overtreated with insulin and occasionally in emaciated cats receiving enteral or parenteral nutrition (Justin and Hohenhaus, 1995; Adams et al., 1993). Hyperphosphatemia is often seen in azotemic patients, but seldom requires special considerations when formulating fluid therapy. Hypermagnesemia and hypomagnesemia are reported. The clinical significance of minor alterations is uncertain,

Table 5–4. Expected Findings and Compensation in Normal Dogs with Simple Acid-Base Disturbances

	pH	Primary Abnormality	Normal Compensatory Response
Metabolic acidosis	↓	↓ HCO_3	↓ Pco_2 by 0.7 mm for each 1 mEq/L ↓ in HCO_3
Metabolic alkalosis	↑	↑ HCO_3	↑ Pco_2 by 0.7 mm for each 1 mEq/L ↑ in HCO_3
Respiratory acidosis	↓	↑ Pco_2	
Acute			↑ HCO_3 by 1.5 mEq/L for each 10 mm ↑ in Pco_2
Chronic			↑ HCO_3 by 3.5 mEq/L for each 10 mm ↑ in Pco_2
Respiratory alkalosis	↑	↓ Pco_2	
Acute			↓ HCO_3 by 2.5 mEq/L for each 10 mm ↓ in Pco_2
Chronic			↓ HCO_3 by 5.5 mEq/L for each 10 mm ↓ in Pco_2

but marked changes can cause a variety of clinical problems, including cardiac arrhythmias, neuromuscular signs, and inability to correct hypokalemia. Extrapolating from human medicine, renal and gastrointestinal losses may be major mechanisms of hypomagnesemia. Excessive intake of magnesium, especially by patients with renal dysfunction, may be a major cause of hypermagnesemia (Brautbar and Massry, 1987).

Acid-Base Status

Changes in acid-base status are important because of the effects that acidemia and alkalemia may have on the body. Evaluation of acid-base status is best accomplished by blood gas analysis. When evaluating blood gas values, one should first determine if the pH is abnormal (DiBartola, 1992b). If it is, there must be an acid-base abnormality. If the pH is normal, there might still be a disorder, but it would have to be a mixed disorder (i.e., two separate disorders occurring simultaneously, such as a respiratory alkalosis due to pulmonary parenchymal disease plus renal failure causing a metabolic acidosis). The reader is referred to other references for information on mixed disorders (see Autran de Morais, 1992b).

If the pH is abnormal, one must next determine if it is due to a metabolic or a respiratory problem (Table 5–4). Remembering that the body does not overcompensate should help one determine what the primary disorder is. (That is, if both the HCO_3 and the Pco_2 are decreased, one should look at the pH to determine the primary problem. If the pH is acidic, it is a partially compensated metabolic acidosis. If the pH is alkalotic, it is a partially compensated respiratory alkalosis.) The next question is whether there is appropriate compensation for the primary disorder. For the dog, there are guidelines to determine if the compensation is appropriate or not (see Table 5–4); however, one cannot extrapolate these guidelines from the dog to the cat. Finally, one should seek the cause of the acid-base disorder (DiBartola, 1992b).

Metabolic Acidosis

Metabolic acidosis is probably the most common canine and feline acid-base disorder that needs to be addressed by the clinician. The most common causes of metabolic acidosis in these species are listed in Table 5–5. Lactic acidosis is one of the most common causes of acidosis. Whenever there is poor peripheral perfusion, anaerobic metabolism may predominate with subsequent production of acid (Hindman, 1990). The acidemia is not actually due to dissociation of the lactate; the lactate simply reflects the anaerobic metabolism that has released protons. Therefore, lactic acidosis may by seen in conjunction with other disorders. Rarely, lactic acidosis may be due to abnormal metabolism by tumors. Lactic acidosis is usually diagnosed by elimination of other causes of acidosis and finding a disease that would cause it. Blood lactate levels may be measured, but this is rarely required. Calculation of the anion gap may help diagnosis as lactic acidosis may cause an increased anion gap (DiBartola, 1992d; Rose, 1984h; DiBartola et al., 1994).

Some patients with profuse diarrhea may lose excessive amounts of bicarbonate in the feces and thereby become acidemic. This typically causes a hyperchloremic metabolic acidosis, which, if an anion gap is calculated, will be associated with a normal anion gap. This acidosis may be combined with lactic acidosis in some patients because of concomitant dehydration. Neither type of acidosis predictably occurs in all or even most diarrheic dogs or cats, however, especially if there is concurrent vomiting (DiBartola, 1992d).

Renal failure causes acidosis when the kidneys cannot adequately excrete H^+, regenerate HCO_3^-, or both. Renal ammonium excretion is the principle means of eliminating protons, and this function is usually adequate until the renal failure becomes severe. Acidemia secondary to uremia may have a normal anion gap initially, but an increased gap is expected in more severe uremia. Hypoadrenocorticism produces acidemia because aldosterone is needed to stimulate secretion of H^+ into collecting duct fluid. Thus, it may be thought of as a functional renal failure. There are also specific renal tubular defects (i.e., renal tubular acidosis) that are uncommon in dogs and cats but that may cause a hyperchloremic acidemia with a normal anion gap (DiBartola, 1992d).

Table 5–5. Common Causes of Metabolic Acidosis

- Lactic acidosis due to decreased perfusion
  - Dehydration
  - Poor cardiac output
- Renal failure
- Diabetic ketoacidosis
- Hypoadrenocorticism
- Addition of acid to the body
  - Ethylene glycol intoxication
  - Salicylate intoxication
  - Ammonium chloride

Diabetic ketoacidosis occurs when there is excessive production of ketone bodies, especially β-hydroxybutyrate. An increased anion gap is expected. If the patient is dehydrated and there is poor renal perfusion, lack of renal excretion of ketones may accentuate the acidosis (as well as produce lactic acidosis) (Nelson, 1995).

When ethylene glycol is ingested, it is metabolized by the liver to glycolic acid. This often results in severe acidemia that is difficult to treat because acid continues being produced until all of the ethylene glycol is metabolized (Clay and Murphy, 1977). This acidosis occurs long before there is any evidence of renal failure. History may be informative, and one can test serum for ethylene glycol. Calcium oxalate crystals may be seen in the urine before renal failure occurs; however, it is easy to mistake calcium oxalate crystals for hippurate crystals. Furthermore, there are monohydrate and dihydrate forms of calcium oxalate crystals, and the clinician must be able to identify either. If checked soon after toxin ingestion (which is when therapy needs to be started to maximize chances of success), one may find a markedly increased anion gap and osmolal gap (Grauer et al., 1984). By the time renal failure occurs, these gaps may be gone, as well as any chance of saving the animal.

Salicylate intoxication is less common than these other causes. It typically results in a mixed acid-base disorder (Rose, 1984h).

Metabolic Alkalosis

Clinically significant metabolic alkalosis in dogs and cats is usually due to vomiting of gastric contents, inappropriate administration of diuretics, or excessive administration of bicarbonate or other alkalinizing agents (e.g., lactate). There are other causes of alkalemia (e.g., severe hypokalemia, severe hypomagnesemia) that are clinically less important (Rose, 1984g; DiBartola, 1992c).

Vomiting of gastric contents causes loss of H^+ as well as loss of Cl^- and water. Hypovolemia plus hypochloremia prevent the relative excess of bicarbonate from being excreted in the urine because the body preferentially restores ECF volume. To restore ECF volume, the body must reabsorb fluid from the renal tubules. To reabsorb this fluid, it must reabsorb sodium. To reabsorb positively charged sodium (a cation), it must reabsorb an equal amount of negatively charged ions in order to maintain electroneutrality. This means that it is necessary to absorb either Cl^- or HCO_3^-. If there is inadequate Cl^- present to allow the body to absorb all the sodium it needs, the body will absorb bicarbonate instead, even though the body already has an excess of bicarbonate (DiBartola, 1992c). A similar pathophysiology occurs when excessive furosemide administration results in vigorous diuresis with chloride-rich urine. Both of these are considered chloride-responsive alkaloses because administration of chloride is crucial to resolving the problem. Clinically important chloride-resistant alkalosis is uncommon in dogs and cats (DiBartola, 1992c).

Respiratory Alkalosis

Respiratory alkalosis is relatively common; hyperventilation due to any cause (e.g., excitement, pain, fear, difficulty maintaining normal oxygenation) eliminates excessive carbon dioxide and can produce alkalemia (Rose, 1984i). Rarely, this alkalosis is the first indication of gram-negative septicemia (Autran de Morais, 1992b). The alkalosis itself, however, rarely causes detrimental effects to the patient and the clinician simply needs to identify the underlying cause.

Respiratory Acidosis

Respiratory acidosis is uncommon in dogs or cats, except for animals that are not being properly ventilated while under anesthesia. Carbon dioxide diffuses through the pulmonary parenchyma much more easily than oxygen, and hypoventilation is one of the few abnormalities that causes this acidosis. Hypoventilation may be caused by airway obstruction, respiratory center paralysis, muscular weakness that prevents breathing (e.g., myasthenia gravis, hypokalemia, botulism), muscular rigidity that prevents breathing (e.g., tetanus, seizures), problems with the chest or pleural cavity that prevent normal respirations (e.g., pneumothorax, pleural effusion, flail chest), and chronic obstructive pulmonary disease (e.g., emphysema) (Rose, 1984j).

Blood Gas Analysis

Blood gas analysis is the best means to evaluate acid-base status. It requires precise technique and good laboratory support. Readers intending to use blood gas analysis extensively should do additional research on the subject to avoid technical errors that easily invalidate results (DiBartola et al., 1994; DiBartola, 1992b). Hand-held, "point-of-care" units have made this analysis feasible for most practices. However, many individuals choose to use the serum total CO_2 measurements (Tco_2) to estimate acid-base abnormalities. When plasma or serum is handled in a normal, aerobic fashion, the Tco_2 closely approximates the serum bicarbonate concentration (DiBartola et al., 1994).

Although Tco_2 is less expensive and is more widely available than blood gas analysis, relying on the measure requires the clinician to make assumptions that may be incorrect for a given patient (DiBartola et al., 1994). One must guess if an abnormal bicarbonate concentration is due to a metabolic or a respiratory abnormality. This guess can often be made accurately by considering history, physical examination, and other laboratory data. Abnormal bicarbonate values are often primary events, representing metabolic acid-base disorders. Even when this assumption is correct, however, one still does not know if appropriate compensation is occurring or what the blood pH is. It is reasonable to rely on the Tco_2 as long as (1) the apparent acid-base abnormality is consistent with what the clinician expects from the patient, based on history, physical examination, and other laboratory data; (2) the Tco_2 is more than 14 and less than 35; and (3) the patient is not severely depressed or experiencing significant cardiac problems.

FLUIDS

Calculation

Administration of fluids involves calculating the amount that a patient is expected to need. This requires consideration of maintenance needs, deficit, and ongoing losses.

Maintenance Fluid Needs

Maintenance fluid requirements (i.e., the amount of fluid necessary to replace insensible losses and obligatory urinary losses) vary with the size of the animal and its diet (i.e., eating a diet containing excessive solutes such a sodium make the patient require more water for maintenance). Ambient temperature and humidity also affect maintenance requirements. There is controversy about the optimal formula for determining the maintenance needs of dogs and cats. In general, smaller animals need more milligrams per kilogram per day than do larger animals. A good rule of thumb is 20 to 30 mL/lb per day for animals between 20 and 100 lb, with smaller animals needing the higher amounts (Muir and DiBartola, 1983; Bell and Osborne, 1992). For animals weighing less than 20 lb or more than 100 lb, one can be more precise by using the formula: $97 \times \text{body weight}^{0.655}$ (Rivers and Burger, 1989). Water is present in foods, however, and is generated as foods are metabolized. Thus, any animal that is eating adequately may need less fluid than calculated by this formula.

The combination of variables makes it difficult to know exactly how much fluid an animal needs. In general, as long as the clinician administers a reasonable amount of fluids and carefully monitors the patient, clinically significant problems are unlikely. It is often better to administer slightly more fluid than is believed necessary because it is more common to underestimate needs than to overestimate them, and dogs and cats can usually be relied on to excrete excess free water. Patients with severe cardiovascular disease or failure, oliguria or anuria, severe anemia, severe hypoalbuminemia, or pulmonary edema, however, need to be monitored very carefully because excessive fluid administration can be fatal.

Deficit Fluid Needs

Fluid deficit must be estimated for most patients when they are initially examined. Although there are guidelines for estimating deficit (Table 5–6), there are many pitfalls in this approach. Any excited or dyspneic animal that is breathing through its mouth may have dry, tacky oral mucous membranes, whereas nauseated animals may have moist membranes despite dehydration. Weight loss causes some degree of skin tenting in many animals, but obese animals may not have skin tenting even when they are 8% to 10% dehydrated (DiBartola, 1992e).

One may measure the hematocrit and the plasma proteins as an aid to assessing dehydration. Because one rarely knows what these values were shortly before the animal became ill, however, they are often less informative than desired. Many animals with chronic diseases will have anemia of chronic disease; dehydration may cause them to have a normal hematocrit. Likewise, many animals will be hypoproteinemic due to gastrointestinal, hepatic, or renal disease, and dehydration may cause them to have a normal serum protein concentration. Animals that are hemoconcentrated and hyperproteinemic are usually dehydrated. There are many reasons, however, why a normally hydrated dog or cat may be hyperproteinemic despite being normally hydrated (e.g., heartworm disease, ehrlichiosis, chronic dermatitis, feline infectious peritonitis). In the same way, weight may be useful if one knows what the weight was immediately before the current problem. Finally, the history is often overlooked when assessing dehydration. Any animal that is not drinking or eating but has ongoing losses, especially those in excess of normal (e.g., vomiting, diarrhea, polyuria, tachypnea) is or will soon be dehydrated.

Table 5–6. Determination of Degree of Dehydration

Manifestation	Degree (%)
Loss of skin elasticity	5
Oral mucous membranes becoming tacky	6–7
Prolonged capillary refill time	6–8
Skin tenting that persists	8–10
Eyes sunken back into orbits	10
Cool extremities, early shock	10–12

In general, because of the problems associated with determination of the degree of dehydration, it is often best to slightly overestimate the deficit if one is unsure (unless the patient has the problems mentioned under maintenance fluid requirements). Deficit is determined by the formula:

$$\text{Body weight (kg)} \times \text{estimated percentage dehydration} = \text{liters needed}$$

Deficit fluids can be administered more quickly than maintenance fluids. If the patient is not in shock, deficit fluids can be replaced over 4 to 8 hours. In general, one should not exceed 90 mL/kg per hour unless the animal is in severe hypovolemic shock. Cats, which have smaller blood volumes per body weight than dogs (i.e., 70 mL/kg vs. 90 mL/kg in the dog), can be overhydrated with lesser amounts than dogs. Once the estimated deficit is replaced, the animal should be reassessed, and one may decide if additional deficit fluids are needed. One should also carefully weigh the patient before and during fluid administration to aid in monitoring ongoing losses (DiBartola, 1992e).

Ongoing Losses

Ongoing losses can be divided into normal, insensible losses (e.g., from respiration) and those that are not normal (e.g., vomiting, diarrhea, polyuria, fever, tachypnea). Whereas insensible respiratory losses involve water but not electrolytes (i.e., "free water"), abnormal losses often involve electrolytes as well as water. Therefore, one must be aware of what kind of fluid loss has occurred when choosing a fluid to administer. Careful assessment of body weight (i.e., with an accurate scale that measures ounces or tenths of a pound) is one of the best means of monitoring for ongoing losses. Because the body is normally 60% water, rapid changes in body weight usually reflect changes in body water content as opposed to muscle mass or fat. One liter represents approximately 1000 mL of water.

Choice of Fluid

There are several categories of fluid and additives available (Table 5–7) (DiBartola, 1992e). Crystalloid solutions (e.g.,

Table 5–7. Selected Fluids and Fluid Additives Commonly Used in Dogs and Cats

- Crystalloids
  - Physiologic saline solution (0.9% saline, PSS)
  - Hypertonic saline (7%)
  - Lactated Ringer's solution
  - Ringer's solution
  - 5% Dextrose in water
  - 0.45% Saline plus 2.5% dextrose
- Colloids
  - Plasma
  - Dextran 70
  - Hetastarch (hydroxyethyl starch)
- Additives
  - Potassium chloride
  - Potassium phosphate
  - 50% Dextrose
  - Sodium bicarbonate
  - Calcium chloride
  - Calcium gluconate
  - Magnesium sulfate

PSS [0.9% saline solution], 5% dextrose in water [D5W], Ringer's solution) are composed of electrolytes and nonelectrolytes that can eventually enter all body compartments. Balanced crystalloids, also called *replacement solutions* (e.g., lactated Ringer's solution [LRS]) have a composition resembling extracellular fluid. Metabolism of the lactate in LRS provides alkali to the body. Unbalanced crystalloids (e.g., PSS, D5W) do not resemble extracellular fluids. One type of unbalanced crystalloid solution is the maintenance solution (e.g., Normosol-M and 5% Dextrose), which typically has less sodium and more potassium than replacement solutions. It is important to note that whenever fluids are administered to provide maintenance needs, potassium in excess of what is found in replacement fluids is needed. Markedly hypertonic crystalloid solutions (e.g., 7% saline solution) may be used in selected cases, such as for certain types of shock. One should avoid crystalloids containing preservatives (e.g., benzyl alcohol), especially for cats, which may have adverse effects from these substances (Ryan, 1982).

Colloidal solutions (e.g., plasma, dextran, hetastarch) contain substances that are more confined to the blood-vascular compartment and thus draw fluids from the cellular and interstitial compartments into this compartment (DiBartola, 1992e). Therefore, although both colloids and isotonic crystalloids can be used to rapidly expand the blood-vascular compartment in animals in shock, colloids are generally more effective and at lower doses than crystalloids (Tobias and Schertel, 1992). It generally requires two to four times as much isotonic crystalloid solution to expand the ECF compartment as much as dextran or hetastarch. Hetastarch is also useful for maintaining plasma tonicity in patients with severe hypoalbuminemia. Dextrans can, however, cause problems in some patients. Dextran 70 may cause intravascular sludging of blood, and both dextran 40 and dextran 70 may produce anaphylactic reactions as well as interfere with blood cross-matching and coagulation function. Therefore, some clinicians consider dextrans contraindicated for patients at risk for acute renal failure. Hetastarch may also cause coagulation abnormalities, but they have not yet been determined to be clinically significant.

If a crystalloid is chosen, the particular fluid to be used is determined by what one is trying to replace. Hypertonic crystalloids (e.g., 3% to 7% saline) are used to rapidly expand the blood volume in patients in shock. They act much like colloids (i.e., cause cellular and interstitial fluids to enter the blood-vascular compartment), but they also have direct cardiac inotropic effects. They do not, however, maintain this volume expansion for as long as colloids (i.e., <2 hours for hypertonic crystalloids vs. up to 36 hours for hetastarch) because the sodium is redistributed to the interstitial compartment. Combining hypertonic saline with 6% dextran 70 prolongs the beneficial effects. If excessive amounts of hypertonic saline are administered, hypernatremia may result. Hypertonic saline should not be used for patients with hypernatremia, severe dehydration, or uncontrolled hemorrhage.

Administration of D5W essentially results in giving the patient free water because the liver rapidly metabolizes the glucose. Administration of D5W almost never, however, significantly contributes to meeting the patient's caloric needs (D5W has 170 kcal/L). The one exception is the patient that has persisting hypoglycemia (DiBartola, 1992e).

Replacement crystalloids (e.g., LRS) are often preferable when replenishing hypovolemia in a dehydrated patient without major electrolyte abnormalities. Physiologic saline solution is often used in this situation, but it is not as good as LRS because it has proportionally more chloride than is found in the plasma. Once the patient is rehydrated, maintenance solutions are preferred for long-term fluid therapy. If a fluid specifically designed to be used for maintenance (e.g., Normosol-M and 5% Dextrose; Table 5–8) is not available, alternating a balanced electrolyte solution (e.g., LRS) with D5W (both with supplemental potassium) in a ratio of one volume of electrolyte solution and two volumes of D5W is often acceptable (DiBartola, 1992e).

Clinicians often need to tailor a fluid for a specific patient. This is usually done by adding potassium chloride, 50% glucose, potassium phosphate, calcium gluconate, calcium chloride, sodium bicarbonate, or a combination thereof. The specific amounts are discussed under specific disorders. Warming the fluids (or at least ensuring that they are not cold) before administration helps prevent hypothermia.

Route of Administration

Fluids may be administered orally, intravenously, subcutaneously, intraosseously, or peritoneally (Hansen, 1992). Whenever oral administration is inadequate (i.e., refusal to drink adequate volumes, vomiting, absorption is not quick enough for desired effect), parenteral administration is preferred. Intravenous administration is the quickest way to replenish a deficient ECF and is the standard means for acute replacement of severe losses (e.g., due to shock) or maintaining ECF volume during anesthetic procedures. This route allows constant infusion, which can be advantageous, particularly to ill animals. One must, however, be

Table 5–8. Electrolyte Composition of Commercially Available Fluids

	Glucose (g/L)	Sodium (mEq/L)	Chlorine (mEq/L)	Potassium (mEq/L)	Calcium (mEq/L)	Magnesium (mEq/L)	Buffer (mEq/L)	Osmolality (mOsm/L)
D5W	50	0	0	0	0	0	0	252
D10W	100	0	0	0	0	0	0	505
PSS	0	154	154	0	0	0	0	308
PSS + D5W	50	154	154	0	0	0	0	560
½PSS + D5W	50	77	77	0	0	0	0	406
½PSS + D2.5W	25	77	77	0	0	0	0	280
Ringer's	0	147.5	156	4	4.5	0	0	310
LRS	0	130	109	4	3	0	28	272
LRS + D5W	50	130	109	4	3	0	28	524
Normosol-R	0	140	98	5	0	3	50	296
Normosol-M and 5% Dextrose	50	40	40	13	0	3	16	364

Abbreviations: D10W = 10% dextrose in water; D5W = 5% dextrose in water; D2.5W = 2.5% dextrose in water; PSS = physiologic (i.e., 0.9%) saline solution; LRS = lactated Ringer's solution; ½PSS = 0.45% saline solution.

Modified from Chew DJ, DiBartola SP: Manual of Small Animal Nephrology and Urology, p 308. New York, Churchill Livingstone, 1986.

able to place and maintain the catheter. This can be difficult because of the patient's size or temperament or prior use of veins for catheters or venipuncture. Furthermore, these catheters must be maintained so that phlebitis does not occur and the catheter remains patent. Finally, because of the immediate access to the blood-vascular compartment, it is possible to administer fluids or electrolytes (especially potassium or calcium) too quickly and harm the patient.

Subcutaneous (SC) administration is technically easier than IV administration and is usually adequate when the need for fluids is not severe or acute. Owners can usually be taught to do this at home. From 50 to 200 mL may be injected per site, and several sites may be injected at one time. If too much is administered at one site, it may not be well absorbed. One should plan on giving the SC injections two to four times daily. If fluid from the prior injections has not been absorbed, however, one needs to determine why before more fluids are administered. Severely dehydrated animals may absorb SC fluids very slowly because of poor peripheral vascular perfusion. Furthermore, one must not administer hypertonic or irritating solutions because they can draw fluids from the central compartment into the SC or cause a large sore, respectively (Hansen, 1992).

Intraperitoneal (IP) administration allows one to give large volumes of fluids that are usually absorbed more quickly than would occur with the SC route. This route is occasionally used for neonates in which a vein cannot be accessed with a catheter. One should administer a warmed, isotonic fluid, aseptically with a 23- to 20-gauge needle. One may administer fluids relatively quickly (i.e., over 1 to 3 minutes) until the abdomen becomes obviously distended, the animal is uncomfortable, or respiratory difficulty due to pressure on the diaphragm occurs. Care must be taken to avoid introducing bacteria. In general, IP administration does not offer clear advantages over IV, IO (intraosseous), or SC routes, which are preferred.

Intraosseous administration has recently been "rediscovered" in veterinary medicine (Otto and Crowe, 1992). It is accomplished by using either a specifically designed needle, a bone marrow aspiration needle, or, in some cases, an 18- to 20-gauge spinal needle. The needle is inserted into the marrow cavity of the humerus, femur, tibia, or ilium. Fluids are then administered constantly as for intravenous administration. Gravity drip rates of approximately 10 mL/min may be reached. Absorption is quicker than occurs with SC-administered fluids, and it may be easier to obtain access to the marrow cavity in very small animals than the jugular or cephalic vein (Fiser, 1990; Okrasinski et al., 1992; Hansen, 1992; Otto and Crowe, 1992). Pain may result from infection, administration of cold solutions, or excessive administration rates.

Water may be administered rectally as an enema because the colon will absorb water infused into its lumen. Currently, this approach is almost never used to provide fluids to patients; IV and IO fluids are required for patients in shock, whereas SC fluids are so easy to administer that there is no reason why someone cannot utilize them. Rectal administration may conceivably, however, be appropriate in selected emergencies.

Determining Adequacy or Inadequacy of Fluid Therapy

Close monitoring of body weight is useful to determine the efficacy of fluid therapy. One is rarely certain, however, what the weight was before the patient became dehydrated. Any physical evidence of dehydration (e.g., skin tenting, dry oral mucous membranes) should resolve if fluid therapy is adequate (assuming there is not another reason for them such as weight loss or tachypnea). One should also check for moist crackles in the lung fields (indicating early pulmonary edema) and new cardiac murmurs or gallop rhythms that indicate cardiac overload.

Urine output should be normal (20 to 45 mL/kg per day). Although this is seldom quantified, it should be obvious that the patient is producing reasonable volumes of urine that are not extremely concentrated. Of course, this is not reliable for patients with renal failure. Measuring central venous pressure is useful but seldom necessary except for seriously ill animals that are rapidly receiving large volumes of fluids or for those with significant cardiac or renal disease (DiBartola, 1992e). If needed, central venous pressure may be measured with a manometer made for this purpose, or one may use a jugular catheter line.

ELECTROLYTES

Considerations for Therapy

Therapy for electrolyte disorders primarily consists of supplementing electrolytes or decreasing the plasma concentrations by increasing excretion or diluting or sequestering the electrolyte. The major electrolyte disorders that the small animal clinician must treat symptomatically are hypokalemia and hyperkalemia. It is rare that one must symptomatically treat hyponatremia. Hypoadrenocorticism is relatively common, but volume replacement and lowering of potassium are usually the major goals for such patients in a crisis. Symptomatic hypernatremia is, fortunately, uncommon in dogs and cats.

Hyponatremia

Hyponatremia is usually due to retention of free water, although loss of sodium is occasionally responsible (e.g., diarrhea). Unless the hyponatremia is severe enough to cause clinical signs that must be addressed, one should first identify and correct the cause. If the hyponatremia is causing significant clinical signs and must be corrected first, administration of sodium-containing fluids at maintenance rates is usually adequate. Do not correct severe hyponatremia too quickly as there is a risk of myelinolysis. Clinical signs may occur 3 to 4 days after aggressive correction of hyponatremia and may include weakness, ataxia, quadriparesis, and/or hypermetria (O'Brien, 1994). Balanced crystalloids such as LRS are often preferable to PSS for this purpose. This is because plasma normally has approximately 145 mEq Na/L and 110 mEq Cl/L. Physiologic saline solution has 154 mEq of each per liter, while LRS has 130 mEq Na/L and 109 mEq Cl/L. Normosol-R is similar to LRS. Therefore, administration of PSS adds too much chloride relative to the amount of sodium, although this is seldom clinically significant. It is rare that hypertonic saline solutions are needed to replace sodium in small animals (Rossi and Schrier, 1987; DiBartola, 1992a).

Hypernatremia

Spontaneous hypernatremia is almost always due to loss of free water, although very rare patients will have ingested too much sodium. Administration of free water by giving D5W is the treatment of choice. Lowering the plasma sodium concentration too fast may, however, be more detrimental to the patient than the hypernatremia. If the hypernatremia has existed for more than a few hours, it is usually best to use a mixture of PSS plus 5% dextrose in water. A mixture of equal portions provides an isotonic solution of 2.5% dextrose plus 0.45% saline. Such a solution decreases the tonicity of the plasma more slowly and lessens the chance for cerebral edema. If necessary, one may tailor other such fluids by combining other ratios of PSS and D5W (DiBartola, 1992a; Rose, 1984k).

Hypochloremia

Hypochloremia is principally found in patients with excessive losses due to gastric vomiting or diuretic administration. Administration of PSS with or without potassium chloride is usually adequate to replace the chloride and resolve the problem.

Hyperchloremia

When hyperchloremia is due to loss of free water, administration of free water via D5W, as discussed for hypernatremia, is adequate for resolution. One must ensure that, if the patient has a *corrected* hyperchloremia due to hypoadrenocorticism, the patient is treated with PSS and steroids and not with D5W, which may make the hyponatremia, and the patient, worse.

Hypokalemia

Supplemental administration of potassium has become routine in small animal medicine because hypokalemia is a common abnormality. Almost every anorexic animal on maintenance fluids should receive greater than replacement amounts of potassium because there are obligatory losses of potassium into the urine. Animals with polyuria or other avenues of potassium loss may have even greater needs. Only those pets that have or are prone to hyperkalemia should not receive potassium supplementation. One cannot confidently predict exactly how much potassium a particular patient will need; hence, the patient's plasma potassium concentration should be periodically monitored when receiving supplemental potassium.

If the patient can accept oral fluids and is not vomiting, oral administration of potassium gluconate elixir is probably the quickest and most efficient means of replenishing plasma potassium (Fournier et al., 1987). This is especially true for cats in which IV fluid administration usually augments urinary losses and initially worsens the hypokalemia, even with fluids containing 30 or 40 mEq K/L. The amount of oral potassium to administer is not well defined. Severely hypokalemic cats often tolerate 2 to 6 mEq K given twice daily (Dow et al., 1987a and b, 1989). Severely hypokalemic dogs may be given 2 to 40 mEq K/day, depending on their size. If oral potassium is being administered to maintain (as opposed to replenish) the patient, lesser amounts often suffice if the patient does not have abnormal losses. Oral potassium chloride salt must be administered carefully (i.e., "light" salt); it is easy to administer too much and cause hyperkalemia.

Intravenous supplementation of potassium is common but demands consideration and monitoring. Administration is usually kept to less than 0.5 mEq/kg per hour, although patients can sometimes receive greater rates without problem. If it seems necessary to administer 0.5 mEq K/kg per hour or more, constant electrocardiographic monitoring for cardiotoxic effects (i.e., bradycardia, heart block, diminished R-wave amplitude) is recommended. Tables (e.g., Table 5–9) are probably the most common means of determining how much potassium to add to fluids for IV administration. Alternatively, one can calculate and administer 0.1 to 0.2 mEq K/kg per hour in mild to moderately hypokalemic patients and 0.2 to 0.4 mEq K/kg per hour in severely hypokalemic patients (Willard, 1989), but this approach is cumbersome and has no real advantage. Fi-

Table 5–9. Approximate Amount of Potassium to Add to Fluids for Intravenous Administration

Serum Potassium (mEq/L)	mEq Potassium to Add to Fluids	Maximum Rate of Infusion (mL/kg/h)
3.5–4.0	15/L	30
3.0–3.5	28/L	16
2.5–3.0	40/L	12
2.0–2.5	60/L	8
<2.0	80/L	6

nally, some clinicians routinely start by adding 20 mEq K/L and monitoring the animal's plasma potassium every 48 hours.

Potassium may also be added to fluids intended for SC administration. In general, one should not use solutions with more than 35 mEq K/L for SC administration (DiBartola and Autran de Morais, 1992).

If the clinician experiences difficulty correcting hypokalemia despite seemingly adequate potassium supplementation, the serum magnesium concentration should be checked.

Hyperkalemia

Therapy for hyperkalemia depends on the severity of clinical signs and the magnitude of the hyperkalemia. Always consider the cause of hyperkalemia because it often reflects renal or adrenal disease. If the patient has mild hyperkalemia (e.g., 5.5 to 6.5 mEq/L) that is not a major risk to the patient, one may first determine the cause (e.g., hypoadrenocorticism, renal failure, iatrogenic). Administration of potassium-free fluids dilutes the plasma potassium and often increases renal potassium excretion if the kidneys are functional. Because most hyperkalemic patients are somewhat dehydrated, this fluid therapy is useful for most hyperkalemic patients. If the patient is also hyponatremic (i.e., hypoadrenocorticism), PSS is excellent because it adds sodium. Although LRS is often acceptable because it has less potassium (i.e., 4 mEq K/L) than the plasma of the animal with hyperkalemia (and consequently dilutes the potassium in the blood), it is generally best to use potassium-free solutions, which dilute the plasma potassium faster.

If the patient has severe hyperkalemia (i.e., >8.0 mEq/L) causing cardiotoxicity, more aggressive symptomatic treatment (Table 5–10) may be necessary to prevent cardiac standstill (Willard, 1989). Rapid administration of potassium-free fluids is still important and is usually the first therapeutic step. Sodium bicarbonate should only be given if one knows the acid-base status of the patient or if the patient is dying from hyperkalemia and there is nothing else available to treat the patient. Administration of dextrose and insulin decreases blood potassium concentrations but can also decrease serum phosphorous concentrations, which rarely causes problems (i.e., hemolytic anemia) (Willard et al., 1987). Calcium gluconate, although often discussed, is almost never needed. It does not lower the potassium level but transiently protects the heart until other measures (i.e., fluid administration, sodium bicarbonate, glucose plus insulin) decrease the plasma potassium concentration (DiBartola and Autran de Morais, 1992).

Table 5–10. Symptomatic Therapy for Hyperkalemia

Potassium-free fluids: Physiologic saline solution or 5% dextrose
Calcium gluconate: 0.5–1.0 mL 10% calcium gluconate/kg intravenously (10–15 minutes)
Dextrose and insulin: 0.5 U regular insulin/kg + 2 g dextrose per unit insulin
Sodium bicarbonate: Based on blood gas analysis or 1–2 mEq/kg

Hypophosphatemia

Therapy for hypophosphatemia depends somewhat on whether one is trying to prevent problems due to hypophosphatemia or treat existing problems (e.g., hemolytic anemia). If the patient has a dangerously low serum phosphorous concentration (e.g., 1.0 to 1.5 mg/dL) but does not have clinical signs, a simple rule of thumb is to provide half of the maintenance potassium being given in the IV fluids (assuming maintenance rates are being used) as potassium chloride and half as potassium phosphate (Willard et al., 1987). The patient's serum phosphorous concentration is then monitored two to three times per day until it is out of the danger zone (e.g., serum phosphorous >2.0 mg/dL), at which time the phosphorous supplementation is stopped. If the animal is experiencing hemolytic anemia, then 0.01 to 0.03 mmol phosphate/kg per hour is a reasonable starting point (Justin and Hohenhaus, 1995; Adams et al., 1993; Willard et al., 1987). The patient must be monitored three to four times daily, however, to ensure that the serum phosphorous concentration is increasing and that the serum calcium concentration is not decreasing. Severe, symptomatic hypocalcemia might result from excessive phosphorous administration. Greater rates of phosphorous administration (e.g., 0.06 mmol/kg per hour) are rarely needed to treat hypophosphatemia (Justin and Hohenhaus, 1995).

Hypomagnesemia

If hypomagnesemia needs to be treated or prevented, magnesium sulfate or magnesium chloride may be administered as a 20% (or lower) solution in D5W. A typical dose is 0.75 to 1 mEq/kg/day given IV by constant rate infusion, although 0.15 to 0.30 mEq/kg may be given over 10 to 15 minutes for life-threatening cardiac arrhythmias (Dhupa, 1995).

ACID-BASE STATUS

Considerations for Therapy

In general, one should always attempt to determine the underlying cause of the acid-base abnormality and correct it. If the acidemia or alkalemia is so severe that it puts the patient at significant risk, however, symptomatic therapy is needed.

Metabolic Acidosis

A blood pH below 7.20 puts a patient at severe risk for decreased cardiac output. For such patients, administration of sodium bicarbonate may be considered. The goal of such therapy is to raise the pH to approximately 7.20 or slightly greater, not to correct the pH back into the normal range. If one administers too much alkali initially, one may find that the patient will become alkalemic as the cause of the acidemia (e.g., diabetic ketoacidosis, lactic acidosis) is corrected (DiBartola, 1992d).

Metabolic Alkalosis

Alkalemia is usually important because of the electrolyte abnormalities it causes rather than direct effects of the high pH on the myocardium. Most dogs and cats with clinically important metabolic alkalosis have a chloride-responsive condition (i.e., vomiting gastric contents, excessive furosemide administration in anorexic animals). Correction of volume depletion and supplementation with chloride (e.g., PSS, often plus potassium chloride) is usually adequate to relieve the problem (DiBartola, 1992c).

Respiratory Acidosis and Alkalosis

Respiratory acidosis and alkalosis need therapy directed at the cause of the problem and seldom if ever need symptomatic therapy.

Drugs Used to Correct Acid-Base Abnormalities

The main drugs used to alter blood and body pH are sodium bicarbonate and fluids. In particular, LRS has often been used to treat acidosis. Under normal circumstances, hepatic metabolism of lactate causes consumption and elimination of protons (i.e., H^+), thus raising the pH (DiBartola, 1992d). If the lactate is not metabolized (e.g., the patient already has lactic acidosis), this does not occur, and the lactate in the LRS would neither contribute to acidemia nor alleviate the problem. Even when the lactate is not metabolized, however, expanding the ECF may improve peripheral perfusion, which could correct the underlying problem. Other fluids could, however, be equally effective in accomplishing this.

Sodium bicarbonate ($NaHCO_3$) is the principle drug used to correct acidemia. It works quickly by adding alkali to the system, which titrates H^+. The two important considerations are when to give it and how much to give. Sodium bicarbonate is not always beneficial to acidemic patients. It is controversial for patients with lactic acidosis in whom addition of $NaHCO_3$ sometimes further lowers the pH (Narins and Cohen, 1987; Stacpoole, 1986). When $NaHCO_3$ is added to the blood, a small percentage of it is converted to CO_2 almost immediately. If this CO_2 cannot be exhaled, it will contribute to the acidemia. Therefore, in patients with lactic acidosis, only small amounts of $NaHCO_3$ should be administered and only when there is dire need. Experimentally, a combination of equimolar amounts of Na_2CO_3 and $NaHCO_3$ seems safer and more effective than $NaHCO_3$ alone for patients with lactic acidosis (Bersin and Arieff, 1988). Likewise, the clinician must remember that when $NaHCO_3$ is given to patients with diabetic ketoacidosis, they may be alkalotic after the ketone bodies are metabolized. Fortunately, most patients can deal with alkalosis better than with acidosis.

There are various formulas to help decide how much bicarbonate (HCO_3) to administer (DiBartola, 1992d). The following is suggested for most situations (but *not* for ethylene glycol intoxication, which causes an intense, progressive acidosis that requires more aggressive therapy) when one wishes to administer $NaHCO_3$ in dogs and cats:

$$\text{mEq to administer} = \text{body weight in kg} \times 0.3 \times \text{calculated } HCO_3 \text{ deficit}$$

The body weight is multiplied by 0.3 to approximate the ECF volume (0.27 would be more accurate, but 0.3 is a useful approximation), which is where the HCO_3 will first be distributed. There will eventually be diffusion of HCO_3 into the cells, and additional HCO_3 may have to be administered to re-attain the desired effect in the ECF. For that reason, some clinicians prefer to use 0.5 instead of 0.3.

The calculated HCO_3 deficit is not the same as "base deficit" (a calculation provided by a blood gas analysis). To calculate the HCO_3 deficit, one must first decide what plasma concentration of HCO_3 is desired. It is usually appropriate to aim for a plasma concentration of approximately 14 to 15 mEq/L if the HCO_3 concentration is less than that initially. The patient's HCO_3 concentration is then subtracted from the desired HCO_3 concentration (e.g., 14 mEq/L). The resulting number is the calculated HCO_3 deficit for this patient at this time. Once the total amount of HCO_3 to be administered is calculated, it is administered IV, usually over 1 to 4 hours. After several hours, this HCO_3 will distribute to the ICF as well as to the ECF compartments, and the patient should be re-evaluated to determine if more HCO_3 is needed.

Severe complications due to $NaHCO_3$ therapy are rare. Hypernatremia, ECF volume overload, hypokalemia, hypophosphatemia, paradoxical cerebrospinal fluid acidosis, and decreased ionized plasma calcium concentrations are, however, possible (Hartsfield, 1981). The more aggressive the $NaHCO_3$ therapy, the more likely the side effects appear to be.

Ethylene glycol intoxication often necessitates more aggressive $NaHCO_3$ therapy. Large amounts of acid are produced as ethylene glycol is metabolized to glycolic acid (DiBartola, 1992d); therefore, it may be difficult to give enough $NaHCO_3$ to maintain a safe pH, depending on how much ethylene glycol was ingested. A factor of 0.5 is used instead of 0.3 when the amount of $NaHCO_3$ to administer is calculated, the $NaHCO_3$ is given over 1 to 2 hours, and the blood pH is rechecked shortly after the treatment is finished and again 1 to 3 hours later.

SPECIAL CONSIDERATIONS

Shock

There are several means of classifying shock. In this discussion, shock is divided into hypovolemic, cardiogenic, obstructive, and distributive. Most dogs and cats in shock have hypovolemic shock due to decreased venous return to the heart with subsequent decreased cardiac output and deficient peripheral perfusion and oxygenation. Typical causes include hemorrhage and severe dehydration. Cardiogenic shock is caused by myocardial failure with or without arrhythmias that decrease cardiac output. Obstructive shock is best exemplified by gastric dilation and volvulus, which obstructs the vena cava and hepatic portal veins, thus preventing venous return. Septic shock is a type of distributive shock in which there is a hyperdynamic cardiac output plus low systemic vascular resistance. It is considered distributive because there is often not a deficit of total body water; rather, the fluids are maldistributed, causing inadequate perfusion. Recently, *systemic inflammatory response syndrome* has been suggested as a better term than *septic shock* because evidence of sepsis may be missing in patients that appear to have endotoxic shock due to occult sepsis. Other examples of distributive shock include anaphylaxis, pancreatitis, heat stroke, and neurogenic shock. To appropriately treat a patient in shock, one must know what type is present (Tobias and Schertel, 1992; Schertel and Muir, 1992).

Hypovolemic Shock

The immediate need is to re-establish effective circulating blood volume. The optimal therapy would be to administer fresh, whole blood. Alternatively, plasma would also be an excellent choice. These are, however, seldom available or cost effective. Balanced crystalloids (e.g., LRS) are commonly chosen because they are available and their high sodium concentration keeps the fluids in the ECF, where they are needed. Initial administration is at 40 mL/lb per hour for the first hour. The patient is then re-evaluated and further fluids are given as needed (Schertel and Muir, 1992).

Other options are colloids or hypertonic crystalloids. Hypertonic (7%) saline may be given in small amounts (i.e., 4 to 5 mL/kg over 5 to 10 minutes) and repeated in increments of 2 mL/kg as needed, up to a total dose of 10 mL/kg. This solution draws ICF into the plasma space and quickly re-establishes effective blood volume. It should then be followed up with a reduced rate of isotonic crystalloids (e.g., 5 to 10 mL/lb). Hypertonic saline should be used cautiously or even be avoided for patients that are already hypernatremic or that have cardiogenic shock. Colloids are sometimes used with hypertonic saline (i.e., dextran 70) or instead of hypertonic saline (i.e., 6% hetastarch) because colloids usually have a longer duration of action in the vascular space than hypertonic saline. Hetastarch is given at a dose of 5 to 20 ml/kg in dogs and 5 ml/kg in cats over 5 to 10 minutes, although one may give up to 40 mL/kg per day. To avoid hypervolemia, the rate of infusion of isotonic crystalloids should be decreased by 40 to 60% after colloids are used (Tobias and Schertel, 1992; Schertel and Tobias, 1992; Okrasinski et al., 1992; Rudloff and Kirby, 1999).

Steroids have been recommended for these patients, but their use is controversial. It seems unlikely that reasonable doses are harmful, but it is not clear that they benefit the patient. Antibiotics are not clearly beneficial but appear reasonable for patients with severe hypovolemic shock because the resulting poor perfusion may allow bacterial translocation across the intestine into the systemic circulation. It is uncommon that vasopressors are needed for hypovolemic shock. In particular, one should avoid α-agonists that increase blood pressure by causing vasoconstriction. Such drugs may increase blood pressure but lessen peripheral perfusion (Tobias and Schertel, 1992).

Obstructive Shock

Gastric dilation/volvulus is the most commonly seen example of obstructive shock. It is treated the same as hypovolemic shock with either isotonic or hypertonic crystalloids (Allen et al., 1991). It is imperative, however, that once fluid therapy has been initiated, steps be taken to relieve the gastric distention that is causing the obstruction (Tobias and Schertel, 1992). Because reperfusion appears to be an important mechanism of injury, oxygen radical scavengers may eventually become important in the early treatment of this disorder. Glucocorticoids are of dubious use for obstructive shock but may be used. One should, however, generally avoid using both steroids and nonsteroidal anti-inflammatory drugs (e.g., flunixin).

Cardiogenic Shock

Patients with cardiogenic shock are best treated by managing the cardiac disease, often with antiarrhythmic or ionotrophic drugs or a combination thereof. One should ensure that fluid therapy does not overload the heart and decompensate the patient; maintenance rates or less are commonly used. For these patients, it often becomes important to give decreased amounts of sodium in order to avoid overloading the ECF compartment (e.g., 0.45% NaCl plus D2.5W) (Ware, 1992). Central venous pressure measurement can be particularly useful in monitoring these patients.

Distributive Shock

Distributive shock is principally seen in animals with septic shock, now better described as *systemic inflammatory response syndrome* (SIRS). In SIRS, release of various inflammatory mediators causes abnormal blood flow regulation with subsequent tissue hypoxia, even when there is normal to increased cardiac output (hence the term *hyperdynamic* shock). If disseminated intravascular coagulation occurs, there may be worsening of hypoxia to affected tissues. Increased vascular permeability may cause plasma volume to leak into interstitial tissues, further reducing tissue perfusion (Haskins, 1992; Jafari and McCracken, 1992; Weeren and Muir, 1992; Bone, 1992).

It can be difficult to effectively treat a patient with SIRS. Blood volume should be maintained as for hypovolemic shock. Either isotonic or hypertonic crystalloids may be used. One must also seek to eliminate the cause of the inflammation, which usually means aggressive antibiotic therapy. Additionally, therapy to decrease the inflammatory response and the generation of the inflammatory mediators responsible for the symptomatology is appropriate. Intuitively, steroids would seem useful, but they have not been shown to clearly benefit these patients, and massive dosages might be detrimental (Lefering and Neugebauer, 1995). Nonsteroidal anti-inflammatory drugs (e.g., flunixin meglumine) may be helpful, especially when administered very early (e.g., 2 hours) in the course of disease associated with *Escherichia coli* endotoxin (Stegelmeier et al., 1988; Hardie et al., 1987); however, further clinical trials are needed to confirm or deny their clinical usefulness.

Hypoglycemia is relatively common, and IV glucose supplementation may be needed. Administering glucose-containing fluids (e.g., D5W or D2.5W) at maintenance rates (approximately 66 mL/kg per day) is usually more than adequate to maintain blood glucose concentrations of more than 100 mg/dL. It is advantageous if patients can receive nutrition during this time because they are generally hypermetabolic. Furthermore, enteral nutrition helps to maintain the integrity of the intestinal mucosa, preventing bacterial translocation from the intestines to the systemic circulation (Haskins, 1992; Jafari and McCracken, 1992; Weeren and Muir, 1992; Bone, 1992).

Renal Disease

Fluid therapy for patients with renal failure should first correct significant fluid, electrolyte, and acid-base abnormalities and then produce a diuresis to eliminate normally excreted substances that have been retained. One must distinguish between polyuric versus oliguric or anuric renal failure and between chronic versus acute renal failure. Severely hypoproteinemic patients with nephrotic syndrome present special challenges. Oliguria means that a patient cannot produce more than 1 to 2 mL urine/kg per hour, although some clinicians use lesser amounts (e.g., <0.25 mg/kg per hour) as the cut-off (Grauer and Lane, 1995). Anuria is a more severe situation in which there is negligible urine production. Polyuria refers to greater than normal amounts of urine being produced. Most patients with chronic renal failure have polyuria until they are preterminal, when they may become oliguric. Patients with acute renal failure may be polyuric or oliguric/anuric. Nephrotic syndrome refers to patients with protein-losing nephropathies that are hypoalbuminemic and usually have ascites, hypercholesterolemia, or both (Polzin et al., 1989).

Polyuric Renal Failure

The first goal of fluid therapy for patients with polyuric renal failure is to correct dehydration (which is commonly present with decompensated renal failure) and severe electrolyte or acid-base abnormalities. If the patient is seriously ill, IV fluids are usually preferred to avoid delayed uptake from SC depots or vomiting of orally administered fluids. For decompensated patients, the next step is usually to increase urine production to a greater than normal rate by IV fluid administration. In this way, dehydration is prevented despite increased urine losses, and the inadequate renal function is compensated for by the larger than normal volumes of urine being produced.

For induction of a fluid-overload diuresis, as much fluid as possible should be administered without overhydrating the patient. The amount of fluid administered each day is slowly increased as the kidneys adapt to the increased demand placed on them. As a general rule of thumb, therapy is begun by replacing deficits and weighing the patient. Then fluids are administered at 1.5 to 2 times the calculated maintenance rate (or more, if necessary to keep up with renal losses). If the patient does not inappropriately gain weight and does not have signs of cardiovascular overload (i.e., gallop rhythm, murmur, pulmonary crackles), one can slowly increase the amount of fluids administered each day, usually by 15% to 30%. Although loop diuretics (e.g., furosemide) are sometimes also required, overload with balanced crystalloids usually produces an adequate diuresis. When one wishes to stop such a volume-overload diuresis, the rate of IV fluid administered is slowly decreased (e.g., 10% to 25%) each day, and the body weight is closely monitored to prevent the patient from becoming excessively dehydrated (Chew, 1992). Although recording central venous pressure and the amount of urine produced per 24 hours are useful, this is seldom required for patients with polyuric renal failure. Some patients also, however, require an osmotic diuretic administered via a central catheter (use of a peripheral catheter may produce phlebitis) to produce an adequate diuresis (see following discussion).

Oliguric and Anuric Renal Failure

Oliguric and anuric renal failure are more difficult to manage than polyuric renal failure. They occur in severe acute renal failure and in terminal chronic renal failure (Grauer and Lane, 1995). In the latter situation, there is usually little that can be offered to help the patient. In the former situation, it is important to try to quickly convert the oliguria to polyuria by replacement of the fluid deficit and then administration of furosemide, osmotic diuretics, and dopamine. Osmotic diuresis may be attempted by administration of 2 mL of 20% dextrose/min IV for 10 to 15 minutes and then decreased to 1 mL/min. A total dose of 25 to 50 mL/kg is anticipated. One should be able to detect glucose in newly formed urine. When the dextrose administration is finished, a balanced electrolyte solution equal to 3% to 5% of the patient's weight is administered. This cycle is repeated two to three times per day as needed until the azotemia is decreased to clinically acceptable levels. The body weight should be monitored closely to avoid excessive overhydration. Plasma electrolytes should also be monitored.

If urine is not produced or if new urine does not have glucose in it, one should stop the infusion before overhydration, pulmonary edema, and hypertonicity occur (i.e., before half of the total calculated volume is administered). Osmotic diuresis may also be attempted by administration of 0.5 to 1.0 g mannitol/kg IV over 15 to 30 minutes with a 10% to 20% solution, but 15% to 20% glucose is recommended because it can be metabolized if it cannot be excreted (Grauer and Lane, 1995).

These patients are simultaneously predisposed to hyperkalemia and severe acidosis, which should be anticipated. Serum magnesium abnormalities are also common. If the patient remains oliguric or anuric, one should administer fluids at maintenance rates and carefully watch for overhydration. One must also monitor body weight and look for signs of cardiovascular overload.

Because these animals are typically difficult to manage, it is often useful to monitor central venous pressure (Allen, 1991). If it is 12 to 14 cm H_2O or higher or if the pressure increases suddenly, one should decrease or stop the fluid administration. Furosemide administration is reasonable. Another technique is to measure urine output and administer fluids accordingly, using a technique sometimes called "ins and outs" (Chew, 1992). One first rehydrates the patient. One next divides the day into four to eight equal intervals. Daily insensible losses (approximately 10 mL/lb per day) are divided by the number of intervals, and that amount is administered over each interval. In addition, one measures the amount of urine produced over an interval and then administers that much fluid back into the animal during the next interval. Unless care is taken, it is easy to overhydrate oliguric patients. If life-threatening overhydration occurs, one may acutely remove blood via a jugular vein to circumvent cardiac failure.

The healing phase of acute renal failure may be accompanied by an intense diuresis that can require administration of several times the calculated daily maintenance volume. Therefore, if an oliguric or anuric patient becomes polyuric, one must guard against dehydration. The rate of fluid administration must be slowly decreased when the patient is being weaned off IV fluids (Grauer and Lane, 1995).

Urethral Obstruction

When urethral obstruction is first detected, the goals are to relieve the obstruction and to quickly correct fluid, electrolyte, and acid-base abnormalities. Severely ill patients usually are dying of hyperkalemia, which may have to be corrected before anything else is done. Administration of potassium-free fluids (e.g., PSS, 5% dextrose in water) will usually dilute the potassium and re-establish renal perfusion so that no other specific therapy for hyperkalemia or acidosis is needed (Stone and Barsanti, 1992). These patients often develop severe polyuria; this is probably the most common cause of diuresis occurring as the kidneys heal after an episode of acute renal failure in small animal practice. The severity of this polyuria will depend on how badly the kidneys were damaged during urethral obstruction. It is common for severely affected patients to have daily fluid needs exceed their calculated maintenance values during this healing period (Stone and Barsanti, 1992).

Nephrotic Syndrome

Nephrotic syndrome has been defined several ways; the definition used here is a protein-losing nephropathy sufficient to cause hypoalbuminemia. When choosing fluid therapy, one must consider both the need for diuresis and the effects of further dilution of serum albumin concentrations by aggressive administration of crystalloids and effects on blood pressure (Polzin et al., 1989). The patient may already have edema, ascites, or pleural effusion due to the hypoalbuminemia. Further dilution of plasma albumin concentrations by IV fluids may worsen these problems. If the third space fluids (i.e., peritoneal or pleural effusions) must be removed, it is best to judiciously administer furosemide in small doses (1 mg/lb once or twice daily). The diuretic causes fluid loss from the vascular compartment that is gradually replaced by fluid from the third space. If too much fluid is removed from the vascular compartment too quickly, renal hypoxia and damage may result (Polzin et al., 1989). The fluid should not be withdrawn with a trocar or needle unless the patient is severely compromised from pleural effusion. Such withdrawal, especially if repeated, will further lower the body albumin concentration and make reaccumulation of fluid more likely.

If the patient's cardiovascular status is rapidly deteriorating due to severe hypoalbuminemia or if one must perform a procedure (especially one requiring anesthesia) in a patient with marginal cardiovascular status, one may administer plasma, albumin, or colloid (e.g., hetastarch). The ability of albumin to maintain blood-vascular compartment expansion is, however, usually gone within 24 to 72 hours, whereas the effects of hetastarch administration are greater and often last 24 to 36 hours. Therefore, plasma and albumin administration should be reserved for patients that must undergo anesthesia or some other procedure and need the effects of the colloid immediately. Even then, use of hetastarch should be considered in place of plasma or albumin (DiBartola, 1992e).

Heat Stroke

Heat stroke occurs when a patient is exposed to excessive heat and has free water loss resulting in severe hypernatremic dehydration. The severe heat can affect the central nervous system, liver, kidneys, and other organs. The dehydration contributes substantially to renal failure, gastrointestinal hypoxia, and disseminated intravascular coagulation. It is imperative to cool the patient off quickly via cold water sprays, enemas, IV fluids, or a combination thereof (Haskins, 1995). Then, aggressive fluid therapy initially with shock doses of approximately 40 mL/lb per hour are suggested to restore effective circulating volume (Rushlander, 1992). It is often wise to start with an isotonic, half-strength PSS plus 2.5% dextrose and later switch to PSS or LRS.

Cardiac Disease

Most animals with cardiac failure do not need parenteral fluid therapy. Animals that are eating and drinking can usually be managed by offering distilled water and using diuretics as needed. However, if the patient is severely dehydrated, is anorexic, or has concurrent renal failure or other organ failure, fluid therapy may be needed. Treatment of such animals in severe cardiac failure is similar to the treatment of those with oliguric renal failure; one must be careful not to overhydrate the patient. Measurement of central venous pressure is useful; however, pulmonary wedge pressure (obtained by use of a Swan-Ganz catheter) offers information not available from the central venous pressure and is desirable for critically ill patients. Excessive sodium administration can be avoided by use of dextrose solutions or dextrose plus half-strength PSS. Administration of excessive sodium can cause fluid overload because these patients are often unable to adequately excrete sodium. Likewise, sodium bicarbonate should be avoided because of the sodium load associated with its administration (Bonagura and Lehmkuhl, 1992).

Electrolyte abnormalities in patients with cardiac disease must be treated carefully. Oral potassium supplementation is best for hypokalemic animals if there is no vomiting. Hypokalemic patients have more toxicity from digitalis and generally have more problems with supraventricular arrhythmias (DiBartola and Autran de Morais, 1992). Marked hyponatremia is usually an indication that the cardiac disease needs to be better managed. Sodium administration is only appropriate for patients with severe, symptomatic hyponatremia. Even then, only enough sodium to alleviate or prevent central nervous system signs should be administered.

Patients with simultaneous cardiac and renal failure are among the most difficult to manage. One must identify the cause of the renal and the cardiac disease and treat each. If the underlying causes cannot be determined or treated, one should optimally monitor central venous pressure, pulmonary wedge pressure, and "ins and outs" while giving small amounts of fluids with minimal amounts of sodium (Bonagura and Lehmkuhl, 1992). In general, fluids are administered as rapidly as possible without excessively increasing the central venous pressure (i.e., >12 to 14 cm H_2O).

Gastrointestinal Disorders

Acute Vomiting

Acute vomiting commonly causes fluid deficits (Johnson, 1992). The severity of the deficit will depend on the severity and cause of the vomiting and on whether the animal will eat or drink. Although vomiting is considered an alimentary tract disorder, many vomiting animals have extra-gastrointestinal disorders (i.e., renal failure, adrenal failure, hepatic failure, hypercalcemia, pancreatitis, diabetic ketoacidosis). The therapy for most animals with moderate to severe, acute vomiting includes not being fed or watered until the vomiting diminishes, which means that the patient has ongoing losses (both insensible and from vomiting) and no intake. Therefore, even if such an animal is not dehydrated at the time of examination, it will usually become so shortly.

If mild dehydration is present or anticipated, SC fluids are often adequate. If the dehydration is or will probably become severe or if the animal appears to be going into shock, however, IV fluids are mandatory. Until the electrolyte and acid-base status are known, PSS or lactated Ringer's solution is usually an acceptable fluid. Although hypokalemia is common in animals with acute vomiting, supplemental potassium should be administered carefully until it is known that the patient is not hyperkalemic from adrenal or renal dysfunction. One of the most common causes of severe vomiting in young animals is parvovirus enteritis, which will be discussed later with acute diarrhea.

Chronic Vomiting

Most patients with chronic vomiting (i.e., lasting 2 weeks or longer) are not dehydrated when presented to the veterinarian. The fact that the animals have had the disease for so long usually means they were able to compensate for their fluid losses. If they had not been able to compensate, they would have been presented earlier as emergencies (i.e., in hypovolemic shock) or would have died. Some of these patients will be dehydrated because of a recent worsening of their disease. Even when the animal's fluid status is acceptable, however, there may be significant electrolyte and acid-base abnormalities.

Fluid therapy must be tailored for each individual. Hypokalemia is common if the patient does not have adrenal insufficiency or severe renal failure (both of which can cause chronic vomiting). One cannot, however, accurately predict what a given patient's acid-base status is, even when the cause of the vomiting is known. Animals with high intestinal obstruction occasionally have a hypokalemic, hypochloremic, metabolic alkalosis that supposedly reflects gastric outflow obstruction, while some animals with seemingly pure gastric fluid losses have a normal pH or are acidotic. If therapy must begin before the electrolyte and acid-base status are known (i.e., the patient is severely dehydrated), then PSS or lactated Ringer's solution is usually acceptable. The danger in supplementing potassium before knowing the patient's electrolyte status is that the patient might have hypoadrenocorticism or severe renal failure, in which case potassium administration could be disastrous. If it is known or strongly suspected that hypoadrenocorticism and severe renal failure are not present (e.g., failure to respond to previous steroid therapy, adequately concentrated urine), one can reasonably add 20 mEq KCl to each liter of fluids administered at maintenance rate (Johnson, 1992).

Acute Diarrhea

Many animals with acute diarrhea are not dehydrated unless the diarrhea is profuse, vomiting is present, or the patient is anorexic. Acute parvovirus enteritis is an important cause of acute enteritis that produces diarrhea, vomiting, and anorexia in many patients. In such a severe case, IV fluid therapy is mandatory regardless of the cause (Johnson, 1992). Treatment initially should address hypovolemic shock, septic shock, or both, if present. Then, until the chemistry panel returns, one may reasonably administer PSS plus 20 to 40 mEq KCl/L at maintenance rates. In parvovirus enteritis, one must also be concerned with hypoglycemia (discussed later), which may occur due to sepsis. One cannot predict the acid-base changes of dogs with parvovirus enteropathy; therefore, do not administer bicarbonate without laboratory evidence of acidosis (Heald et al., 1986).

Chronic Diarrhea

Most patients that are presented to the veterinarian because of chronic diarrhea are not dehydrated. The fact that the animals have had diarrhea for so long and are just now being examined usually means that they were able to compensate for their fluid losses. If they had been unable to maintain hydration during the previous 2 or more weeks, they probably would have been presented earlier as emergencies, or they would have died. A recent worsening of the disease may, however, cause dehydration in which case it is reasonable to start fluids (usually PSS supplemented with 20 mEq KCl/L) while waiting for serum chemistry panel results. Hypokalemia is the most common electrolyte problem in these patients, and acute renal failure and hypoadrenocorticism (two of the most common causes of noniatrogenic hyperkalemia) seldom cause disease characterized predominantly by diarrhea. The acid-base status cannot be predicted, and one should not administer alkalinizing solutions until at least the T_{CO_2} is known.

Another major concern for animals (especially dogs) with chronic diarrhea is hypoalbuminemia. Protein-losing enteropathies may produce serum albumin concentrations of less than 1.5 g/dL, which can be associated with ascites and loss of fluids from the effective circulating volume (Johnson, 1992). The clinician should avoid excessively diluting the remaining albumin in severely hypoalbuminemic patients, which would result in further pooling of fluid in third spaces and depletion of effective circulating volume. If the animal needs increased oncotic pressure, plasma may be administered. It is common, however, for albumin that has been administered IV to be lost rapidly into the intestines of animals with protein-losing enteropathies. Hetastarch is often effective for longer times because it is not lost into the intestinal lumen as quickly.

Pancreatic Disease

Acute Pancreatitis

Acute pancreatitis is a potentially fatal disease that has no specific therapy in most cases. Affected dogs usually are anorexic and yet vomit gastrointestinal secretions, leading to severe dehydration. The primary therapies available are withholding oral intake (to prevent further stimulation of the pancreas) and fluid therapy (to allow pancreatic perfusion) (Johnson, 1992). If an inflamed pancreas is poorly perfused, the inflammatory state may progress from a relatively mild, edematous one to a severe, hemorrhage, necrotic condition with a poor prognosis.

The most common mistakes in treating patients with pancreatitis are feeding too soon and inadequate administration of fluids (Williams, 1995). Not only must the fluid deficit be replaced, but one must also attain a normal effective circulating volume so that visceral perfusion is improved. It is important to recognize the difference between restoring fluid deficit and improving tissue perfusion. Severe abdominal inflammation may cause fluid to pool in the abdomen or peripancreatic tissues and be useless for pancreatic perfusion. Furthermore, there may be pooling of fluid in the intestinal tract due to poor motility and the nearby inflammation.

It is also important to monitor the serum albumin concentration. If the albumin concentration drops (due to sequestration in the abdomen caused by the inflammation), there can be poor tissue perfusion. In such a case, plasma or hetastarch may be useful. There is also some thought that administration of plasma may replenish circulating proteases that offer some protection against enzymes released from the diseased pancreas (Johnson, 1992).

Diabetic Ketoacidosis

Animals with diabetic ketoacidosis are often but not invariably severely dehydrated and acidotic. Appropriate insulin therapy plus replacement of fluid deficit usually result in success if the patient does not have severe pancreatitis (Nelson, 1995). Reasonable initial choices of fluids include PSS and LRS until laboratory data are obtained. Automatic addition of $NaHCO_3$ to the fluids is dangerous and unnecessary. Many, if not most, ketoacidotic patients will become hypokalemic once therapy is begun; therefore, it is reasonable to start supplementing potassium with the initial fluids (Nelson, 1995). Hypophosphatemia is a potential problem of aggressive insulin therapy, and serum phosphate concentrations must be monitored, especially if anemia is developing. If the patient becomes hypophosphatemic, the IV fluids should be supplemented with potassium phosphate. An initial rate of 0.01 to 0.03 mmol phosphate/kg per hour is reasonable; however, the patient must be monitored to avoid causing hypocalcemia and hyperphosphatemia (Willard et al., 1987). Hypomagnesemia may also occur.

Hepatic Disease

The main concerns about administration of fluids to a patient with hepatic disease are hypoalbuminemia, hypoglycemia, fluid and salt retention, and electrolyte abnormalities. Fluids restricted in sodium (e.g., half-strength PSS plus 2.5% or 5% dextrose) should be used to help avoid fluid retention in patients with chronic hepatic disease prone to ascites (e.g., cirrhosis). Addition of glucose to the fluids (i.e., 2.5% to 5%) guards against hypoglycemia and helps prevent hepatic encephalopathy. If hypoalbuminemia is severe, colloids in addition to crystalloids should be considered. It often requires large volumes of plasma to significantly increase plasma albumin concentrations. Hypokalemia predisposes the patient to hepatic encephalopathy; it can be avoided by supplemental potassium chloride in the IV fluids (Johnson, 1992).

Acid-base abnormalities are difficult to predict and must be assessed in each patient. In general, one should avoid alkalemia because it predisposes to hepatic encephalopathy (Schenker et al., 1974). Therefore, LRS and $NaHCO_3$ should be avoided unless there is a specific indication for them.

Hypoglycemia

Hypoglycemia may be caused by various diseases (e.g., septicemia, hypoadrenocorticism, hepatic insufficiency, insulinoma, starvation of a neonate, iatrogenic overdose of insulin). Regardless of its cause, hypoglycemia that is responsible for signs (i.e., weakness, coma, convulsion) should be treated (Feldman and Nelson, 1987a). For emergencies, 1 to 2 ml of 50% dextrose/kg is drawn up and administered IV slowly, to effect. For a more prolonged effect, one may add dextrose to maintenance fluids. In most cases, 2.5% dextrose given at maintenance rates will maintain the blood glucose concentration in a safe range (i.e., >80 mg/dL). In rare cases, one may need to administer 5% instead of 2.5% dextrose to achieve this goal.

Hypocalcemia

Symptomatic hypocalcemia is usually caused by puerperal tetany, hypoparathyroidism, ethylene glycol intoxication, or inappropriate administration of a hypertonic phosphate enema. Regardless of its cause, hypocalcemia causing clinical signs (i.e., tetany, convulsions) should be treated (Feldman and Nelson, 1987b). Calcium chloride works faster than calcium gluconate but is more dangerous (10% calcium gluconate has 0.46 mEq Ca/ml whereas 10% calcium chloride has 1.36 mEq Ca/ml); calcium chloride causes severe solughing if injected perivascularly, and rapid IV administration may produce cardiotoxicity. Approximately 0.5 to 1.5 mL of 10% calcium gluconate is administered per kilogram, or one can administer 5 to 15 mg/kg slowly, to effect, over 10 to 30 minutes. If calcium chloride is used, one usually only needs to administer 1 to 3 ml per animal. Such a treatment usually lasts a few hours, although some animals will need additional therapy within 1 to 3 hours. Once the crisis is over, one may add calcium to the IV fluids to provide constant infusion. In general, 10 mL of 10% calcium gluconate is added to 500 mL of PSS and administered at maintenance rates. Then, the serum calcium level and clinical signs are monitored and the amount of calcium in the IV fluids increased if needed. Alternatively, one may administer 1 to 2 ml calcium gluconate/kg (diluted 1:1 in sterile PSS) SC (Feldman, 1995).

Hypercalcemia

Symptomatic hypercalcemia in dogs is usually due to pseudohyperparathyroidism, primary hyperparathyroidism, hypoadrenocorticism, vitamin D intoxication, or chronic renal disease causing tertiary hyperparathyroidism (Elliott et al., 1991). It is important to rapidly decrease the plasma concentration of calcium to prevent nephrotoxicity. This is ultimately best accomplished by elimination of the cause (e.g., removing or treating the malignancy causing pseudohyperparathyroidism, removing the parathyroid adenoma). While searching for the cause, however, one may administer excessive volumes (e.g., twice or more maintenance requirements) of PSS to initiate a saline diuresis and enhance urinary calcium excretion (potassium concentrations must be monitored to avoid hypokalemia) (Chew et al., 1992). Furosemide also promotes natriuresis and calciuresis if the patient is adequately hydrated. Administration of 0.5 to 1 mg prednisolone/lb/day may enhance calcium excretion and reduce bone resorption as well as intestinal calcium absorption. However, steroid administration may make it more difficult to diagnose the cause of the hypercalcemia. In severe cases one may also alkalinize the patient with sodium bicarbonate or administer prednisolone, mithramycin (Rosol et al., 1994), calcitonin, or a combination thereof. Calcitonin is especially important in the treatment of animals that have eaten cholecalciferol-containing rodent baits (Garlock et al., 1991).

SURGERY

Dehydration should be corrected before surgery and anesthesia, if possible. Even after deficits have been corrected, animals undergoing prolonged general anesthesia usually benefit from IV fluid support. Unless the patient is hypoproteinemic or anemic, crystalloids (e.g., PSS, LRS) are usually administered at 2 to 5 mL/kg per hour. Severe hypoproteinemia and anemia should be corrected with blood or blood components before the patient is anesthetized.

If one anticipates significant loss of blood during the procedure, the basal rate may need to be increased by 5 to 10 mL/kg per hour. If there is substantial blood loss or the hematocrit falls to less than 20% to 25% during the procedure, strong consideration should be given to administering red blood cells (either as packed red cells or whole blood). If one is attempting to correct for blood loss during the procedure with crystalloids, one should administer approximately three times as much crystalloid solution as one estimates there has been blood loss (Muir, 1992).

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Therapy with Blood and Blood Components

6

Dawn Merton Boothe

BLOOD GROUPS
Antigens
Alloantibodies
DONORS
COLLECTION
Materials
  Receptacles
  Anticoagulants
Collection Procedure
STORAGE AND BLOOD COMPONENTS
Whole Blood and Packed Red Blood Cells
Plasma
Platelets
CLINICAL USE
Blood
  Administration
  Rate
Plasma
Transfusion Reactions
AUTOTRANSFUSION
BLOOD SUBSTITUTES
BONE MARROW TRANSPLANTATION

BLOOD GROUPS

Antigens

The blood cells of each species are grouped according to antigens located on the red blood cell (RBC) surface, which determine the immunologic specificity of the cell. The number of antigens that have been detected varies among species. Although canine blood has been characterized by at least 11 blood groups (Stormont, 1982), 8 are generally recognized and are designated as DEA (dog erythrocyte antigen) 1.1, 1.2, and 3 through 8 (Dodds, 1985). Of these, DEA-1 and DEA-7 are the most common clinically significant antigens.

The cat has three blood groups, designated A, B, and AB. Types A and B of the cat are unrelated to human blood groups. Both groups are allelic, with the A allele expressing dominance over B. The incidence of each blood type is characterized by marked geographic differences both outside and inside the United States; type A is by far the most common, with an incidence ranging from 99% in the United States to 70% in Australia (Cotter, 1991; Giger et al., 1989; Auer and Bell, 1981). The remaining cats have type B, although a very low incidence of type AB (0.4%) has been reported (Auer and Bell, 1981; Giger and Bucheler, 1991; Authement et al., 1987). A small number of cats with type AB blood (≤0.1%) have been identified in the United States. Although type A is also the most common detected in purebred cats, approximately 10% have type B blood. Breeds such as Abyssinians, Persians, Himalayans, and Rex appear to have a higher incidence (Norsworthy, 1992). Some catteries have exclusively type B cats. No Siamese have been reported to have type B. Cats lacking both type A and B antigens have not been identified.

Alloantibodies

Plasma contains allantibodies (isoantibodies) whose activity is directed toward antigens contained on RBCs from animals of the same species. Naturally occurring isoantibodies are genetically determined and are present when an animal receives its first blood transfusion. A transfusion reaction may occur with the first transfusion if the recipient plasma contains isoantibodies directed toward the donor RBC antigens. A less severe reaction can occur if the donor plasma contains isoantibodies directed toward recipient RBCs. The incidence of clinically important natural isoantibodies is low, however, and incompatible antigen-antibody reactions are uncommon with initial blood transfusions (Stormont, 1982; Dodds, 1985). Anti–DEA-7 is the most common isoantibody in dogs, present in about 50% of the canine population. About 45% of blood in dogs tested contain DEA-7 antigen (Cotter, 1991). Shortened survival of DEA-7 blood after transfusion into DEA-7–negative dogs has been documented (Cotter, 1991). Routine cross-matching procedures generally do not, however, test for this reaction (Cotter, 1991).

Although cats with either A or B type have naturally occurring isoantibodies (alloantibodies), the anti-A antibody (type B cats) is stronger and responsible for most serious incompatibility reactions. All type B cats have strong hemagglutinin and hemolysin titers of anti-A alloantibodies (Kristensen and Feldman, 1995). In contrast, cats with type A have low anti-B alloantibodies. In Australia, the blood of approximately 35% of type A cats contains isoantibodies against type B cells. These antibodies are only weakly agglutinating, however, with titers less than 1:2, and thus transfusion reactions are absent or mild (Auer 1981; Giger 1991). Destruction occurs extravascularly due to IgM and IgG. In contrast, approximately 70% of type B cats contain strong isoagglutinins (titer > 1:8) to type A. Thus, cats with type B blood are at a greater risk for serious transfusion reactions (Auer et al., 1981; Giger and

Bucheler, 1991). Cats with type AB blood apparently do not have isoantibodies to either type A or B. Intravascular destruction of RBCs occurs intravascularly and is complement and IgM mediated (Giger and Bucheler, 1991).

In addition to naturally occurring alloantibodies, administration of whole donor blood containing antigens foreign to the recipient will stimulate formation of new alloantibodies directed against donor RBCs. Antigens DEA-1.1 and DEA-1.2 (often referred to as a type A) (Cotter, 1991) are the most likely canine antigens to sensitize a recipient, and crossmatching procedures concentrate on these antigens (Cotter, 1991). For example, administration of blood containing DEA-1.1 antigens to a DEA-1.1–negative recipient will result in the formation of anti–DEA-1.1 antibodies in the recipient. Formation of new antibodies will take 10 to 14 days. Approximately 25% of random primary (i.e., first) transfusions in dogs may result in DEA-1 antibody formation in the recipient animal (Tangner, 1982). As a result, the recipient may develop a delayed transfusion reaction to the first transfusion, or severe immunologic reactions can develop upon subsequent readministration of DEA-1 blood.

The incidence of transfusion reactions after a random second blood transfusion has been estimated to be 15% in the dog (Stormont, 1982; Dodds, 1985). The potential of a foreign antigen to stimulate antibody production formation varies with each antigen. DEA-1.1 and DEA-1.2, which together occur in about 60% of the canine population, have the greatest potential for stimulating antibody production in canine recipients. Thus the administration of blood from DEA-1.1 or DEA-1.2 dogs should be avoided, particularly in animals that may require a second transfusion at a later date. Destruction of transfused red blood cells is accelerated when transfused into incompatible animals. In cats mean survival time (time when one half of the transfused cells have been removed from the circulation) of autologous (from the same animal) washed RBCs is 38 ± 2 days. Mean survival of same-type transfusions (i.e., cat type A receiving type A) is 30 days, whereas that of different types of transfusions is less than 15 days. If type A blood is transfused into a type B cat, the survival time is less than 2 hours (Norsworthy, 1992). Repeated transfusions are characterized by an even shorter RBC mean survival time of less than 5 days (Marion and Smith, 1983a; Turnwald, 1985).

Neonatal isoerythrolysis occurs as red blood cells of the newborn are lysed by maternal alloantibodies that have entered the newborn's circulation from colostrum during nursing. In cats, cases reflect type B blood in the queen and type A in the sire and kittens (Kristensen and Feldman, 1995). Clinical signs include failure to thrive, icterus, and anemia. Kittens should be removed from their mother (for 3 days) and foster nursed. Type B queens should be mated to type B or otherwise compatible sires.

Crossmatching detects the presence of both natural and induced isoantibodies in plasma of either the recipient (major crossmatch) or the donor (minor crossmatch) plasma (Authement et al., 1987). It does not prevent sensitization; rather, it detects that which has already occurred or will occur with transfusion at the time of crossmatching (Cotter, 1991). The major crossmatch is the most important of the two and can be relatively easily performed on fresh blood. Crossmatching is particularly essential for animals with a history of receiving a transfusion within the past 4 days (Dodds, 1985; Lees, 1985; Marion and Smith, 1983b; Cotter, 1991). Feline typing reagents are not readily available. Major crossmatching may, however, detect incompatible transfusions (Cotter, 1991). Commercial "rapid card" tests are available through commercial animal blood banking sources for screening of incompatibilities.

Canine blood typing is available from several laboratories:

Dr. Robert Bull, Department of Medicine, B220 Life Sciences Building, Michigan State University, East Lansing, MI 48824 (517-355-4616)
Stormont Laboratories, 1237 East Beamer Street, Suite D, Woodland, CA 95776 (530-661-3078)
Antech Diagnostic Laboratories, 17672A Cowan Avenue, Suite 200, Irvine, CA 92714 (800-745-4725)
University of Tennessee, Veterinary Teaching Hospital, Box 1071, Knoxville, TN 37901 (615-974-8387)
Eastern Veterinary Blood Bank, 2138-B, Generals Highway, Annapolis, MD 21401 (800-949-3822)

Feline blood typing is also available at the School of Veterinary Medicine, University of Pennsylvania.

The life span of compatible transfused, nonstored RBCs should be similar to that of normal RBCs. Transfusion of incompatible cells can result in immediate destruction or delayed destruction, depending on rapidity of antibody production (see previous discussion). Increased destruction of transfused RBCs at 2 to 21 days has been noted for dogs and cats (Tangner, 1982; Marion and Smith, 1983a). Prolonged storage of RBCs also reduces survivability (Marion and Smith, 1983b).

DONORS

Dogs and cats serving as donors can be owned (housed) at the practice or may be client owned as part of a donor program. Donor programs have proved useful for private and academic practices in large urban areas (Hennes, 1989; Kristensen and Feldman, 1995). With modification, programs could be developed for both cats and dogs for most practices. Canine donors should be young, healthy, and cooperative, with no history of a blood transfusion. Blood collection is easier from short-haired, lean animals. Dogs should weigh at least 20 kg and cats 4 kg (Pichler and Turnwald, 1985; Authement et al., 1987). Cats should have a packed cell volume of at least 35% (Homeida et al., 1986). Dogs preferably should be DEA-1 and DEA-7 negative. Greyhounds are often considered to be the ideal canine donor choice because their incidence of these antigens is low (Authement et al., 1987). Female donors should be neutered. Donor animals should be free of blood-transmitted infections. Dogs should be tested for ehrlichiosis, brucellosis, microfilaremia, hemobartonellosis, and babesia; cats should be tested for leukemia, immunodeficiency and infectious peritonitis virus, toxoplasmosis, and hemobartonellosis. Splenectomy of donor animals to cause recrudescence of enhanced detection of blood-borne diseases is controversial. Routine care for donor animals should include vaccinations, and internal and external parasiticide

Table 6–1. Animal Blood Banking Resource Information*

Animal Blood Banking, PO Box 6211, Vacaville, CA, 95696 (530-678-3009); hotline, 800-243-5759
Eastern Veterinary Blood Bank, 800-949-3822
Hempet, Irvine, CA, 714-252-8455
Midwest Animal Blood Services, 517-851-8244

*Services are available 24 hours a day to provide blood or blood components or to answer questions regarding transfusion medicine.

treatment. Supplemental care for small animal donors should include adequate dietary intake of vitamins (particularly B_{12}, folic acid, and pyridoxine), minerals (iron), and proteins of meat origin. Records should be kept on donors, particularly with regard to date and amount of collections (Pichler and Turnwald, 1985; Lees, 1985).

Several commercial blood banking services now provide prepared blood products to practitioners who do not choose to maintain a donor (or participate in a client-owned donor program) (Table 6–1). These services provide not only overnight delivery of blood or blood components for dogs and cats but also blood-collecting equipment.

COLLECTION

Materials

Receptacles

Two types of containers are available for collection of blood (Authement et al., 1987; Norsworthy, 1992) (Figs. 6–1 and 6–2). Vacuum bottles are simple to use because the vacuum allows collection from the jugular vein in small animals. The bottle is penetrated during collection, however, which may allow bacterial contamination of collected blood. Other disadvantages of glass bottle collection include:

1. Inability to separate blood components (e.g., plasma or platelets)
2. Activation of platelets and some coagulation factors
3. Potential for air embolism
4. Breakage of the bottle.

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Figure 6–1. Vacuum bottles (two sizes are shown) are more convenient to use for blood collection than bags (see Fig. 6–2), but they are associated with greater risks. A blood collection set is in front of the bottles; this must be purchased separately.

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Figure 6–2. The satellite bag *(left)* accompanies the blood collection bag and allows for easy separation and subsequent storage of plasma from red blood cells. However, collection may require sedation.

In contrast, plastic bags remain sterile, separation of components is easy if units with satellite bags are purchased, and activation of blood components is not as likely as with glass. Plastic bags for single-unit small animal whole blood collection are less expensive than glass bottles, especially when the cost of the blood collection set is added to the cost of the bottle. Collection is more difficult into plastic bags compared to glass bottles, however, because positive (i.e., arterial) or negative (i.e., a syringe or a vacuum device) pressure is needed to generate blood flow sufficiently rapid to prevent clotting in the collection tube or bag. Thus,

1. Sedation may be needed in small animals
2. The time necessary for collection is longer
3. Clotting is more likely to occur in the collection tubing
4. Arterial hemorrhage may complicate femoral arterial collection.

Materials designed for blood collection can be purchased from several commercial sources (e.g., Baxter). Products specifically designed for collection from small animals (including small collection bags) can be purchased from Animal Blood Banking (see Table 6–1). A vacuum apparatus is also available from Animal Blood Banking, which precludes the need to use arterial sites for collection into plastic bags in dogs. Small plastic bags designed for collection of blood from cats can also be purchased; however, an anticoagulant must be added to these bags. Syringes can also be used to collect blood for small animals or pediatric animals (Pichler and Turnwald, 1985; Lees, 1985).

Anticoagulants

Anticoagulants used for blood collection include ACD (acid citrate dextrose), CPD (citrate phosphate dextrose), sodium citrate, and heparin (Oberman et al., 1981; Authement et al., 1987; Norsworthy, 1992). Each has its advantages and disadvantages. Maintenance of normal RBC physiology is an important consideration in the selection of the most appropriate anticoagulant.

The RBC undergoes significant changes in physiology during storage. The oxygen-carrying capacity of RBCs changes as ATP and 2,3-diphosphoglycerate (2,3-DPG) content decline. The oxygen dissociation curve thus shifts to the left, and delivery of oxygen to tissues by the transfused blood is decreased. These metabolic changes are, however, largely reversible. Up to 50% of depleted 2,3-DPG is replaced within 24 hours of transfusion, although replacement occurs at the expense of host RBCs (Oberman et al., 1981; Lees, 1985).

In addition to pH and related changes, stored red blood cells may become spherical and rigid and thus less deformable. Once the cells are transfused, their destruction by the host is accelerated if they maintain their abnormal shape (Auer et al., 1982). Acid citrate dextrose (14 mL/100 mL blood) will preserve blood for up to 3 weeks. Citrate phosphate dextrose (14 mL/100 mL blood), however, will preserve canine RBCs better and longer (4 to 6 weeks) due to enhanced preservation of pH, ATP, and 2,3-DPG, and RBC deformability (Pichler and Turnwald, 1985; Lees, 1985). Feline blood can be stored in ACD for at least 30 days (Marion and Smith, 1983b). Acid citrate dextrose can be prepared by diluting a mixture of 1.8 g (3.6 mL) of 50% dextrose, 1.6 g sodium citrate, and 0.5 g citric acid with enough distilled water to make 50 mL. After sterilization by autoclave, the solution will be sufficient for collection of 450 mL blood. Acid citrate dextrose is also commercially available in prepackaged quantities (Blynco Development Company, Sherburn, MN) that can be dissolved in sterile water, sterilized, and used to collect blood (Hunt and Moore, 1990).

Heparin (250 to 625 units/mL) (Authement et al., 1987) is limited to collection of small quantities of blood (50 mL) such as that needed for pediatric patients or cats. Blood collected with heparin cannot be stored (Authement et al., 1987) because heparin contains no preservatives and will be inactivated within 24 to 48 hours. Heparin also activates platelets, rendering them nonfunctional, an undesirable effect if the host is deficient in platelets. Sodium citrate (1 mL of 3.5% solution to 9 mL blood) can also be used for collection of small quantities of blood from dogs and cats. Although sodium citrate contains no preservatives or energy sources, it is rapidly metabolized and excreted and therefore safe to the recipient. Collected blood can be refrigerated up to 35 days before use.

Collection Procedure

A total of 20 to 25 mL blood can be collected per kilogram weight of donor dog every 14 to 21 days. Up to 6 mL per pound or a maximum of 50 mL is recommended for collection from cats (Pichler and Turnwald, 1985; Authement et al., 1987; Norsworthy, 1992). Up to 20% of a donor's body weight (10 to 15 mL/kg) can be collected safely at 2- to 4-week intervals (Hunt and Moore, 1990). This total can be divided into multiple withdrawals during the prescribed time period as long as intervals are at least 7 days for dogs and 10 days for cats.

The jugular vein is the safest and most efficient site of collection in all animals, but in the dog and cat suction or vacuum is needed (Pichler and Turnwald, 1985). The femoral artery can also be used for plastic bag collection from dogs, but this route requires moderate sedation and added care to avoid hemorrhage. Should a sedative prove necessary for blood collection from a donor, there is little to no concern about the sedative effects of the chemical restraint in the recipient. The volume of blood administered to the donor will not contain a sufficient dose of drug to cause pharmacologic effects. Cardiac puncture as a means to collect blood from dogs and cats is contraindicated except in terminal (euthanasia) cases (Pichler and Turnwald, 1985) or in ferrets.

Regardless of the site of blood collection, a sterile preparation is necessary. The puncture must be "clean" to avoid activation of platelets and factors. Blood should be gently mixed throughout collection to equally disperse the anticoagulant. Collected blood should be labeled and dated before refrigeration, and the collection should be recorded in the donor's record. The amount of blood collected can be measured by weight (1 g = 1 mL).

STORAGE AND BLOOD COMPONENTS

Whole Blood and Packed Red Blood Cells

Whole blood or blood components can be either purchased or prepared (Oberman et al., 1981; Kristensen and Feldman, 1995). Whole blood contains all blood constituents with the exception of coagulation proteins (Fig. 6–3*A*). Fresh whole blood is whole blood that is administered within 6 hours of collection; coagulation proteins remain active until that time. Packed RBCs are collected from whole blood that has either undergone centrifugation or has been stored at 10°C until red cells have settled by sedimentation (Fig. 6–3*B*). Blood-collection units with integral transfer containers should be used if preparation of RBCs is anticipated. The removal of 225 to 250 mL of plasma from 500 mL of whole blood will generally result in residual RBCs with a hematocrit between 70% and 80% (see Fig. 6–3). As with whole blood, packed RBCs must be refrigerated at 1° to 6°C and, when stored properly, will have the same expiration date as whole blood. Packed cells with a hematocrit greater than 80%, however, undergo accelerated aging during storage and have a decreased mean survival time after transfusion. Whole blood or packed RBCs must be maintained.

Collected whole blood or packed RBCs should be either used within 24 hours or, in the case of ACD or CPD anticoagulated blood, stored at refrigerator temperatures (1° to 6°C) for the previously described period. Preservation of RBCs can be enhanced by gentle mixing at intervals throughout the storage period and by uniform temperatures. Blood stored in a standard refrigerator should be placed as far back on the shelf as possible to minimize temperature fluctuations, which decrease RBC life span. Refrigerated blood that is subsequently warmed to more than 10° C should be used within 24 hours (Auer et al., 1982; Lees,

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expi *B,*
The whole blood can be centrifuged and separated into its component parts: packed red blood cells *(left)* and plasma *(right)*. Both are labeled with the date of collection, the amount collected, the expiration date, and the animal from which the blood was collected.

1985; Authement et al., 1987; Turnwald, 1985). Methods for collection and preparation of component parts have been described (Authement et al., 1987).

Plasma

Storage requirements for blood component parts (e.g., plasma cryoprecipitate) are different from those for whole blood and packed RBCs. Plasma that has been separated from RBCs can be prepared and stored in several ways (see Fig. 6–3). Fresh plasma must be separated from RBCs and administered within 6 hours of collection. Frozen plasma (which contains electrolytes and proteins such as albumin and fibrinogen) can be separated from whole blood at any time after collection up to the expiration date of previously collected blood.

The factors that are viable, however, depend on the rapidity with which it is frozen after collection as well as on the duration of freezing and the temperature at which it is stored. The vitamin K–dependent factors (II, VII, IX, and X) remain stable in frozen plasma (Cotter, 1991). Fresh frozen plasma differs from frozen plasma in that coagulation factors V and VII also remain stable; however, it must be frozen within 6 hours after collection, preferably at −40° to −80°C. It can be stored at these temperatures for 1 year or in a household freezer for 3 months, at which time it becomes frozen plasma (Cotter, 1991; Authement et al., 1987).

Units of plasma in plastic bags should be stored individually in boxes. A rubber band should be placed around the plasma bag so that a crease is formed during freezing. The rubber band is removed when the unit is frozen. The loss of the crease before administration indicates that the unit has been inadvertently thawed (Authement et al., 1987).

Platelets

Platelets and platelet-rich plasma require centrifugation within 6 hours of collection. Cryoprecipitate contains concentrated sources of coagulation factors VIII, von Willebrand factor, fibrinogen, and fibronectin (Cotter, 1991). It is the white foamy precipitate formed after centrifugation of partially thawed (slurry consistency) fresh frozen plasma that has been frozen for 6 months or less (Authement et al., 1987). When frozen immediately after collection into a satellite bag, the component can be stored for another year at −40° to −80°C. Platelet yield for platelet or platelet-rich plasma is greatest when centrifugation occurs at high speeds (1200 *g*) for a short time (2.5 minutes) at 20°C. After preparation, platelets that are not immediately used should be continuously rocked or intermittently mixed for up to 72 hours at room temperature. Platelets can be stored at 1° to 6°C without agitation for 48 hours (Authement et al., 1987). Refrigerated platelets do not, however, maintain their function or viability as well as those stored at room temperature. Platelet products cannot be stored (Marion and Smith, 1983b).

Platelet-rich transfusions (and blood as needed) are indicated for platelet deficiencies, including immune-mediated thrombocytopenia. Vincristine-loaded platelets (0.01 to 0.025 mg/kg) can be used for patients refractory to therapy targeting immune-mediated disease or idiopathic thrombocytopenia (Green et al., 1982; Helfand et al., 1984). Vinca alkaloids, in addition to immunosuppression, also appear to stimulate megakaryocytes by changing the structure of circulating platelets. In addition, macrophages that phagocytize vincristine bound to circulating platelets will be destroyed. Macrophage turnover may necessitate repetitive treatment. With prolonged use or high doses, vincristine can cause bone marrow suppression.

CLINICAL USE

Blood

Blood transfusion in small animals is indicated in cases of acute hemorrhage or anemia in which the packed cell volume (PCV) is less than 20%. Packed cells are preferred for the normovolemic animal so that the administration of

Table 6–2. Blood Component Storage, Dose, and Administration Rates

Component	Storage	Dose and Administration Rate*
Fresh whole blood	<12 hours (CPDA1)	10 mL/lb will ↑ PCV 10%†
Stored whole blood	37 days (ADSOL), 4°C 21 days (CPDA1), 4°C	10 mL/lb will ↑ PCV 10%†
Packed red cells	37 days (ADSOL), 4°C 20 days (CPDA1), 4°C	5 mL/lb will ↑ PCV 10%†
Platelet-rich plasma	1–3 days (CPDA1), 22°C	0.5 U/10 lb (1 U/10 kg)
Fresh frozen plasma	1 year, −30°C 3 months −18°C	5 mL/lb (10 mL/kg), repeat until bleeding is controlled
Cryoprecipitate	1 year, −30°C 3 months, −18°C	0.5 U/10 lb, repeat until bleeding is controlled
Plasma/cryopoor plasma	5 years, −30°C	5 mL/lb (10 mL/kg), repeat until bleeding is controlled

Abbreviations: ADSOL = commercial additive that prolongs red cell viability; CPDA1 = citrate phosphate dextrose adenine; DIC = disseminated intravascular coagulation.

*All blood products should be administered within 4 hours according to standards set by the American Association of Blood Banks. As per this approximate guideline, blood should be administered according to the target PCV, size, and clinical status of the patient.

†Or calculated more accurately as weight (lb):

$$40 \text{ lb (dog) or } 30 \text{ lb (cat)} = \frac{\text{desired PCV} - \text{patient PCV}}{\text{PCV of donor blood}}$$

Modified from Kristensen AT, Feldman BF: Blood banking and transfusion medicine. In Ettinger SJ, Feldman EC (eds): Textbook of Veterinary Internal Medicine, 4th ed, pp 347–360. Philadelphia, WB Saunders, 1995.

isoantibodies and other foreign protein can be avoided. Blood for therapy of chronic anemia generally is limited to animals with a PCV of less than 10%. Component therapy is indicated for special cases.

Administration

Blood administration requires sterile preparation at the site. Blood should be gently mixed before administration. A blood administration set or other filter should be used to remove clots and large particles (Fig. 6–4; see Fig. 6–3*A*). The filter does not remove microaggregates that may accumulate during storage (Marion and Smith, 1983b). An infusion set with a sidearm lever connecter is available for the administration of blood collected in a syringe for small animals (Marion and Smith, 1983b). A large-gauge intravenous catheter should be used (20 gauge for dogs, 22 gauge for cats, 23 gauge for pediatric patients). Larger needles should be used for administration of packed cells; forcing blood through small-gauge needles results in turbulence that causes hemolysis of RBCs. Whole blood or packed cells may be mixed with normal saline to reduce viscosity (Turnwald, 1985). Coadministration of other fluids should be avoided (Authement et al., 1987; Turnwald, 1985) (Table 6–2).

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Figure 6–4. An example of a blood filter that can be placed on the end of a syringe for administration of small volumes of blood (e.g., to cats or pediatric dogs). The filter used for administration of larger volumes of blood is shown in Figure 6–3*A*.

The site of administration partially depends on patient size. A large vein is preferred. Intraperitoneal administration may be used for pediatric patients. Up to 40% of administered blood will be absorbed in 24 hours and 82% in 1 week (Turnwald, 1985), although the life span of the RBC is probably reduced. Intramedullary (i.e., intraosseous) administration is also recommended for pediatric patients. Usually the femur but often the humerus is the site of administration. Absorption is rapid, with 93% of administered blood absorbed in 5 minutes. Regardless of the site of administration, a filter (80 or 170 μm) should be used to remove macroaggregates that form in blood during storage (see Fig. 6–4). Filters can be purchased as part of a blood administration set (straight type [4C2116] or Y type [4C2197] blood recipient sets, Fenwal Laboratories, Division of Travenol, Deerfield, IL) or separately but adaptable to a syringe for transfusion of smaller volumes (Hemonate Filter).

Blood can be warmed in a 40°C water bath up to 37°C to avoid hypothermia and cardiac arrhythmias in the host animal. Commercially available blood-warming baths and coils are also available (V5420, McGaw Laboratories, Inc., Sabana Grande, Puerto Rico). Care must be taken to not heat blood too rapidly or too high to avoid RBC destruction.

The dose of blood necessary to change the PCV can be calculated based on the patient's body weight and the present PCV (Fig. 6–5; see Table 6–2). Generally, patient PCV and protein do not change until more than 20 mL of blood/kg recipient weight has been transfused. Accurate calculations of total blood volumes necessary to achieve a

PCV of donated blood (cat)

PCV of recipient	30%	32%	34%	36%	38%	40%	42%	44%	46%	48%
4%	16.3	15.3	14.4	13.6	12.9	12.3	11.7	11.1	10.6	10.2
6%	14.0	13.1	12.4	11.7	11.1	10.5	10.0	9.5	9.1	8.8
8%	11.7	10.9	10.3	9.7	9.2	8.8	8.33	8.08	7.6	7.3
10%	9.3	8.8	8.2	7.8	7.4	7.0	6.77	6.42	6.1	5.8
12%	7.0	6.6	6.2	5.8	5.5	5.3	5.00	4.8	4.6	4.4
14%	4.7	4.3	4.1	3.9	3.7	3.5	3.3	3.2	3.0	2.9

A

PCV of donated blood (dog)

PCV of recipient	36%	38%	40%	42%	44%	46%	48%	50%	52%	54%	56%	58%
10%	22.2	21.1	20.0	19.0	18.2	17.4	16.7	16.0	15.4	14.8	14.3	13.8
12%	20.0	19.0	18.0	17.1	16.4	15.7	15.0	14.4	13.8	13.3	12.9	12.4
14%	17.7	16.8	16.0	15.2	14.5	13.9	13.3	12.8	12.3	11.9	11.4	11.0
16%	15.5	14.7	14.0	13.3	12.7	12.1	11.7	11.2	10.8	10.4	10.0	9.7
18%	13.3	12.6	12.0	11.4	10.9	10.4	10.0	9.6	9.2	8.9	8.6	8.3
20%	11.1	10.5	10.0	9.5	9.1	8.7	8.3	8.0	7.7	7.4	7.1	6.9
22%	8.9	8.4	8.0	7.6	7.3	7.0	6.7	6.4	6.2	5.9	5.7	5.5
24%	6.7	6.3	6.0	5.7	5.5	5.2	5.0	4.8	4.6	4.4	4.3	4.1

B

Figure 6–5. The amount of blood (mL/lb) that should be administered to a recipient in order to achieve a post-transfusion packed cell volume (PCV) of 18% (cat) or 30% (dog). The amount to be transfused varies with the PCV of the donor *(across)* and the PCV of the recipient *(down)*. For a recipient cat weighing 10 lb with a PCV of 10%, 7.8 mL of blood/lb or 78 mL total with a PCV of 36% would be required to increase the PCV to 18%. For a 10-lb dog with a PCV of 10%, 22.2 mL/lb or 222 mL of blood from a dog with a PCV of 36% would be necessary to increase the PCV to 30%.

specific post-transfusion PCV in the recipient can be made from the following formula in which milliliters of donor blood is equal to

$$\text{Recipient weight (kg)} \times 90\text{ mL/kg} \times \frac{\text{Desired PCV} - \text{recipient PCV}}{\text{Donor PCV}}$$

where 90 mL/kg (or 70 mL/kg for cats) is the blood volume.

Finally, the amount of blood needed for a transfusion can be roughly but rapidly estimated, assuming a donor PCV of 40% by the following formula: mL donor blood = 1 mL whole blood per pound body weight of recipient per 1% change in PCV desired (Turnwald, 1985). For example, to obtain a PCV of 25% in a 30-lb dog with a PCV of 15%, one would need to transfuse 30 × (25% − 15%) or 300 mL whole blood.

Rate

Regardless of the amount of blood to be transfused, baseline vital signs should be measured and the initial rate of administration should be slow, 0.25 mL/kg during the first 10 to 30 minutes. During this time, the patient should be monitored for volume overload (particularly if it is a cardiac patient) and transfusion reactions. For the remaining period, the rate should be 1 to 5 mL/kg/h, although a rate of 22 mL/kg/h may be used for hypovolemic patients. Fluid therapy is also indicated for the hypovolemic (including shock) patients. A slow rate should be used to administer blood to cardiac patients (e.g., 1–4 mL/kg/h) (Turnwald, 1985).

Plasma

Plasma therapy may be indicated for patients whose serum albumin level is less than 1.5 g/dL or fresh frozen plasma for patients whose clotting factors are deficient. Cryoprecipitate is indicated for hemophilia, von Willebrand disease, and other specific syndromes. Plasma and related products containing foreign proteins should be administered cautiously. Because plasma contains the majority of donor proteins (including antibodies), transfusion reactions are not uncommon and, as with whole blood, may occur with the initial transfusion. Thus, administration should probably be slower than the recommended 2 to 5 mL/kg/h. A total dose of 5 to 10 mL/kg is recommended with each transfusion.

The amount of albumin needed to replace a deficit is difficult to calculate (Kristensen and Feldman, 1995). Normal albumin (40% intravascular + 60% extravascular) = 3.5 g/dL:

Step 1: Normal plasma volume = A = 4.5% of body weight (kg)
Step 2: Normal plasma albumin (g) = 3.5 (g/dL) × A (dL)
Step 3: Patient plasma albumin (g) = patient albumin (g/dL) × A (dL)
Step 4: Plasma deficit = B = normal plasma albumin (g) − patient plasma albumin (g)
Step 5: Total albumin deficit = T = (B/40) × 100 (g)
Step 6: Plasma units needed = T (g)/5 g* = ______

For patients with disseminated intravascular coagulopathy, heparin (10 U/kg) can be preincubated with fresh frozen plasma or cryoprecipitate to activate antithrombin III before transfusion (Kristensen and Feldman, 1995).

Transfusion Reactions

When reactions between donor and recipient cells/antibodies are moderate to severe, the reaction is considered to be a transfusion reaction (Authement et al., 1987). Adverse reactions to blood transfusions can be either immunologically or nonimmunologically (Lees, 1985; Turnwald, 1985) mediated. Immunologic responses include immediate (acute) and delayed (chronic) transfusion reactions. *Acute hemolysis* is due to an immediate reaction between donor and recipient antigens and isoantibodies. It can occur with an initial transfusion, but it is more likely to follow subsequent transfusions. The signs of an acute reaction due to hemolysis include nausea, vomiting, salivation, tachycardia, hypovolemia, prostration, urticaria, and fever. The use of DEA-1–negative and DEA-7–negative blood will reduce the incidence of acute transfusion reactions in dogs. *Delayed transfusion reactions* are likely if an unexplained decrease in the PCV occurs 2 to 21 days after transfusion. These reactions usually occur within 7 to 10 days after transfusion and are more likely with repeated transfusions due to sensitization of the donor to recipient RBC antigens. Jaundice may be present. Crossmatching can help reduce the incidence of acute and delayed transfusion reactions. Reactions can also result from white blood cell antigen-antibody reactions.

Nonimmunologic adverse reactions to blood transfusion include fever, which indicates bacterial contamination of the blood; vascular overload indicated by clinical signs of coughing, dyspnea, vomiting, and pulmonary edema; energy expenditure in the very debilitated recipient after massive transfusion of energy-depleted blood (i.e., after prolonged storage); and air embolism if glass bottles are used (Lees, 1985; Marion and Smith, 1983b). Overdosage of the anticoagulant used in the donor blood may also occur after massive transfusion, thus impairing the recipient's coagulation system. Citrate toxicity has been reported after transfusions of blood containing ACD or CPD. This results from the chelation of recipient calcium by the anticoagulant in the donor blood and is manifested as hypocalcemic tetany. Liver disease in the recipient may exacerbate this problem (Lees, 1985; Authement et al., 1987).

AUTOTRANSFUSION

Autotransfusion involves collection of blood and readministration to the same patient (Niebauer, 1991; Zenoble and Stone, 1978). Blood can be collected from a healthy patient in anticipation of a future need for blood (within 3 weeks). When this technique is used, three to six collections should be made over a 10- to 14-day period. Autotransfusions may also be used for patients suffering hemorrhage into a body cavity from which the blood can be efficiently collected for readministration. Such blood is immediately available and is minimally physiologically affected, and transfusion reactions are avoided. Blood collected from body cavities requires filtering to remove clots and other materials. No anticoagulant is necessary if the blood has been in contact with a peritoneal or pleural surface for longer than 45 minutes. Blood can be simultaneously collected and administered with a butterfly catheter, stopcock, in-line transfusion filter, and syringes (Turnwald, 1985). The major disadvantage of this method is that biogenic amines released by defibrination are not removed from the blood and can cause severe reactions.

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*Approximately 5 g albumin/unit canine plasma.

BLOOD SUBSTITUTES

Two types of blood substitutes are currently being developed for their ability to carry and deliver substantial amounts of oxygen to tissues: free hemoglobin and fluorocarbons (Lowe, 1986; Gould et al., 1985). Free hemoglobin solutions are characterized by a short half-life (20 minutes) and a P_s50 lower than blood, both of which will decrease oxygen availability in tissues. Fluorocarbons are chemicals that are miscible with blood and can carry as much as 5.25 mL of oxygen per 100 mL of blood, depending on oxygen tension. Although the oxygen-carrying capacity of these compounds is not adequate for total blood replacement, their low viscosity makes them potentially useful in disorders characterized by abnormalities in microcirculation. In addition, use of these agents in nonvascular tissue (such as the peritoneal cavity) may enhance supplementing oxygen exchange in tissues during respiratory failure.

Oxyglobin (Biopure Corp., www.oxyglobin.com) is a hemoglobin-based oxygen-carrying fluid derived from polymerized bovine hemoglobin. Oxyglobin increases plasma and total hemoglobin concentrations and thus increases arterial oxygen content. Oxyglobin has an average molecular weight of 180 kD, with 50% of the hemoglobin polymers between 65 and 130 kD. As such, it has colloidal properties similar to those of dextran 70 and hetastarch. Because it is a polymerized hemoglobin, however, the molecules are much larger than hemoglobin, and the compound is not likely to be filtered by the kidney (thus avoiding renal side effects of hemoglobinuria).

Because the hemoglobin has been removed from the red blood cells, antigens from the cell are absent and the risk of sensitization is reduced. The absence of isoantibodies in plasma reduces the risk of an immediate transfusion reaction. Antigenicity to bovine hemoglobin may, however, result in antibodies, and caution is recommended with repeated administration 10 or more days apart. Repeated administration of the product is currently being studied. Because Oxyglobin contains a foreign protein, anaphylactic reactions are possible.

Oxyglobin is eliminated similarly to hemoglobin by reticuloendothelial cells. Its elimination half-life in dogs is estimated to range between 30 and 40 hours. As such, 90% of the drug will be gone within 5 to 7 days after infusion. As a protein, the compound provides oncotic pressure (draw), and its use in patients already suffering from volume overload (e.g., congestive heart failure) or in cases of accidental overdose (>10 mL/kg/h) can be associated with circulatory overload and its negative sequelae (e.g., pulmonary edema, pleural effusion, increased central venous pressure, dyspnea, or coughing).

Oxyglobin mildly decreases PCV immediately after infusion and increases total and plasma hemoglobin concentrations for at least 24 hours. Packed cell volume and RBC counts are not accurate measures of anemia for 24 hours after administration. Adequate hydration is important, but overhydration should be avoided because of the plasma-expanding properties of Oxyglobin. Administration of other colloidal solutions should be avoided. The most likely side effect is circulatory volume overload. Central venous pressure or clinical signs indicative of circulatory overload should be monitored during and immediately after administration of Oxyglobin.

Transient changes or side effects after administration of Oxyglobin reported by Biopure Corp. include yellow-orange discoloration of the skin, sclera, and gums; red to dark-green discoloration of feces; brown-black discoloration of urine; vomiting; diarrhea; and decreased skin elasticity within 48 hours of dosing. The frequency and intensity of these clinical signs are dose-dependent. Oxyglobin is intended as a one-time use only at a recommended dose of 30 mL/kg intravenously at a rate of up to 10 mL/kg/h.

Conditions studied in controlled canine clinical trials included immune-mediated hemolysis (n = 30), blood loss (gastrointestinal, traumatic, surgical, rodenticide intoxication; n = 25), and ineffective erythropoiesis (idiopathic, RBC aplasia, ehrlichiosis; n = 9). Relative to pretreatment, plasma hemoglobin concentration significantly increased ($P = 0.001$) and clinical signs associated with anemia (lethargy/depression, exercise intolerance, and increased heart rate) significantly improved ($P = 0.001$) after treatment with Oxyglobin. Treatment success was defined as the lack of need for additional oxygen-carrying support (i.e., blood transfusion) for 24 hours after the completion of infusion with Oxyglobin. Success in the treatment group was 95% compared with 32% in untreated control dogs.

Oxyglobin may be warmed to 37°C before administration. It cannot be frozen but is stable for 24 months. Care should be taken to avoid temperatures that are too cold in the refrigerator. It is approved for use in dogs but apparently has been studied in and is also safe in cats. The price is about $30/kg, although animals may not need the full 30 mL/kg; according to the manufacturer, 10 mL/kg may be sufficient in some cases. The foil bag in which the product is contained is oxygen-impermeable. Once the bag is opened, oxygen can penetrate the plastic bag, resulting in the oxidation of the hemoglobin and methemoglobinemia. A brown discoloration will appear when approximately 25% of the hemoglobin has been oxidized. The product also offers an excellent environment for bacterial growth, even with refrigeration. The product should be used within 4 days of opening.

BONE MARROW TRANSPLANTATION

Although bone marrow transplantation is not yet clinically practical, it has proved successful and may provide an avenue of therapy for cases of aplastic anemia or pancytopenia (Harris and Beck, 1986). Transplantation requires matching of donor and recipient major histocompatibility gene complex. The recipient must be "conditioned" to receive the graft by total body irradiation so that the tendency to reject the graft is decreased.

Bone marrow is collected from the donor by multiple bone marrow aspirations from long bones with heparin as the anticoagulant. Dimethylsulfoxide is used as the preservative. The marrow is then transfused intravenously. The cell numbers needed for a successful transplantation depend on the degree of donor-recipient gene matching. Complications include host-versus-graft rejection (the host rejects the transplant) and graft-versus-host rejection in which the graft is so successful that it rejects (and kills) the host.

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Drugs Acting on Blood or Blood-Forming Organs

7

Dawn Merton Boothe

- DRUGS STIMULATING RED BLOOD CELL PRODUCTION
  - Red Blood Cell Formation
    - Hematopoiesis
    - Vitamin B_{12}
    - Folic Acid
    - Hemoglobin Synthesis: Iron
  - Erythropoietin
    - Mechanism of Action
    - Disposition
    - Preparations
    - Adverse Effects
    - Clinical Use
    - Therapeutic Failure
  - Granulopoietin and Related Products
  - Anabolic or Androgenic Steroids
    - Chemistry
    - Mechanism of Action
    - Pharmacologic Effect
    - Pharmacokinetics
    - Preparations
    - Toxicity Versus Efficacy
    - Clinical Indications
- DRUGS ACTING ON COAGULATION OR CLOTTING
  - Hemostatic Drugs
    - Topical
    - Systemic
  - Antihemostatic Drugs
    - Anticoagulants
    - Fibrinolytics
    - Antithrombotics

DRUGS STIMULATING RED BLOOD CELL PRODUCTION

Pharmacologic therapy for anemia is oriented toward (1) providing components needed for red blood cell (RBC) production (e.g., proteins, vitamin B_{12}, and folic acid), including hemoglobin synthesis (iron and other minerals); and (2) stimulating bone marrow formation of RBCs.

Red Blood Cell Formation

Hematopoiesis

Hematopoiesis occurs through differentiation of stem cells that are formed early in embryonic life. Differentiation occurs in a series of steps in which burst-forming units (BFUs) and colony-forming units (CFUs) are formed for each of the major cell lines. These undifferentiated cells continue to proliferate and differentiate under the influence of a number of cellular and humoral factors that are produced by bone marrow and peripheral tissues.

Erythropoietin (EPO) is the most important regulator of the proliferation of committed erythroid cells (Hillman, 1996) (Fig. 7–1). The kidney is the major site of EPO production, where it is released in response to anemia or hypoxia. Among the more important regulators of the myeloid series are granulocyte colony-stimulating factor (G-CSF) and granulocyte/macrophage colony-stimulating factor (GM-CSF). Several vitamins are needed for red and white blood cell formation (hematopoiesis and granulopoiesis, respectively) (Adams, 1995; Hillman 1996).

Vitamin B_{12}

Vitamin B_{12} (cyanocobalamin), the "maturation factor," is essential for DNA synthesis, and its deficiency inhibits nuclear maturation and division. Because cells that rapidly multiply are affected first, reduced RBC proliferation and a "maturation arrest" in the bone marrow are among the first indications of a vitamin B_{12} deficiency. The erythroblast cannot continue to divide, becomes very large, and is referred to as a *megaloblast* ("megaloblastic anemia"). The mature erythrocyte is also large and is referred to as a *macrocyte*. Although its oxygen-carrying capacity is adequate, the enlarged cell is very fragile because of its large size, and it has a reduced life span (Adam, 1995; Hillman, 1996).

Vitamin B_{12} is a porphyrin-like compound with a ring containing a centrally located cobalt (Hillman, 1996). It can be acquired from both the diet and microbes in the gastrointestinal tract. Most microbial production is in the large intestine, however, where B_{12} is not readily absorbed. Dietary deficiency of B_{12} is unlikely and usually results from poor absorption (including pancreatic enzyme deficiency) from the gastrointestinal tract. Absorption of B_{12} is complicated (Fig. 7–2) and depends on several factors (Hillman, 1996). Gastric acid and pancreatic enzymes are needed to release B_{12} from dietary and salivary binding proteins (Hillman, 1996). To avoid digestion, B_{12} is protected by binding to intrinsic factor and R protein, which are secreted by the parietal cells. The bound B_{12} complex is carried to the ileum, where B_{12} is adsorbed to highly specific receptor sites on the brush border. Vitamin B_{12} enters the cell by pinocytosis and then enters the blood, where it is bound with transcobalamin, the plasma carrier. Excessive vitamin B_{12} is stored in large quantities in the liver and is slowly released as needed. Vitamin B_{12} is excreted into the bile but undergoes enterohepatic cycling. Interference with absorption by the ileum will result in continuous depletion of B_{12}. Many months of defective vitamin B_{12} absorption are necessary, however, before vita-

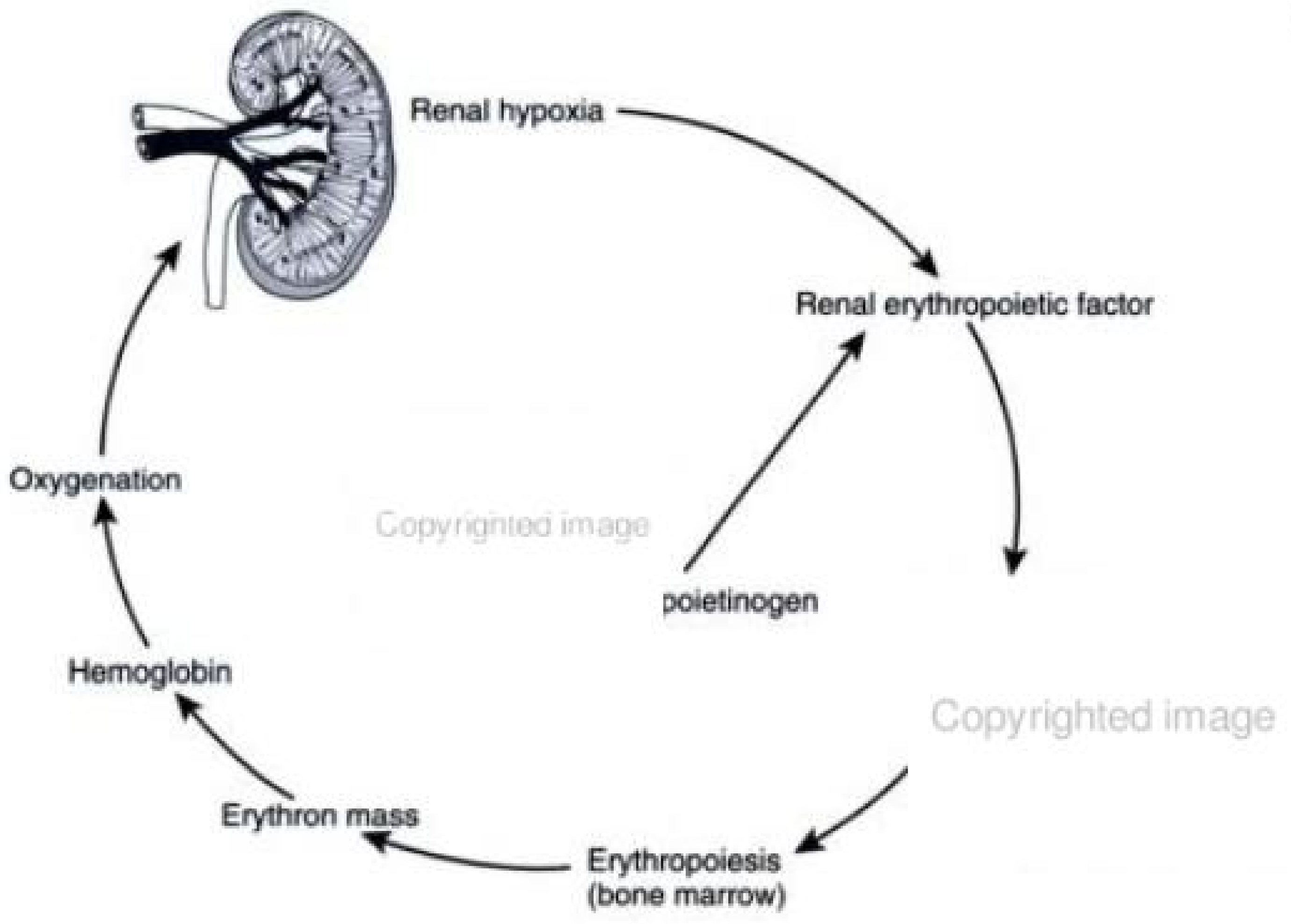

Figure 7–1. Red blood cell formation is stimulated in the kidney. Erythropoietic factor release is stimulated by hypoxia. Erythropoietin stimulates erythroid precursors and the release of reticulocytes into circulation.

min B_{12} deficiency occurs. The anemia resulting from B_{12} deficiency is also referred to as *pernicious anemia*.

Vitamin B_{12} is available as a parenteral preparation in the pure form of cyanocobalamin or the more highly protein bound hydroxocobalamin. Hydroxocobalamin may provide more sustained effects than cyanocobalamin when given by injection (Hillman, 1996). Vitamin B_{12} is also available for oral administration in the pure form or in combination with other vitamins and minerals. Methylcobalamin is another congener of vitamin B_{12} and represents one of the two intracellular active forms of the vitamin (the other being deoxyadenosylcobalamin) (Hillman, 1996). Foods high in vitamin B_{12} include selected microbial sources and animal (meat) products. There are no significant toxicities associated with therapy. Indications for B_{12} therapy are limited to situations of B_{12} malabsorption such as ileectomy, gastrectomy, malabsorption syndromes, or chronic administration of cimetidine or other antisecretory drugs because an acid environment is necessary for release of B_{12} from the diet and for intrinsic factor activity.

Folic Acid

Folic acid (pteroylglutamic acid) is a cofactor needed for DNA synthesis because it promotes the formation of a nucleotide necessary for DNA formation. Folic acid is also necessary for RNA synthesis, and it serves as a methyl donor for the formation of vitamin B_{12} (Hillman, 1996).

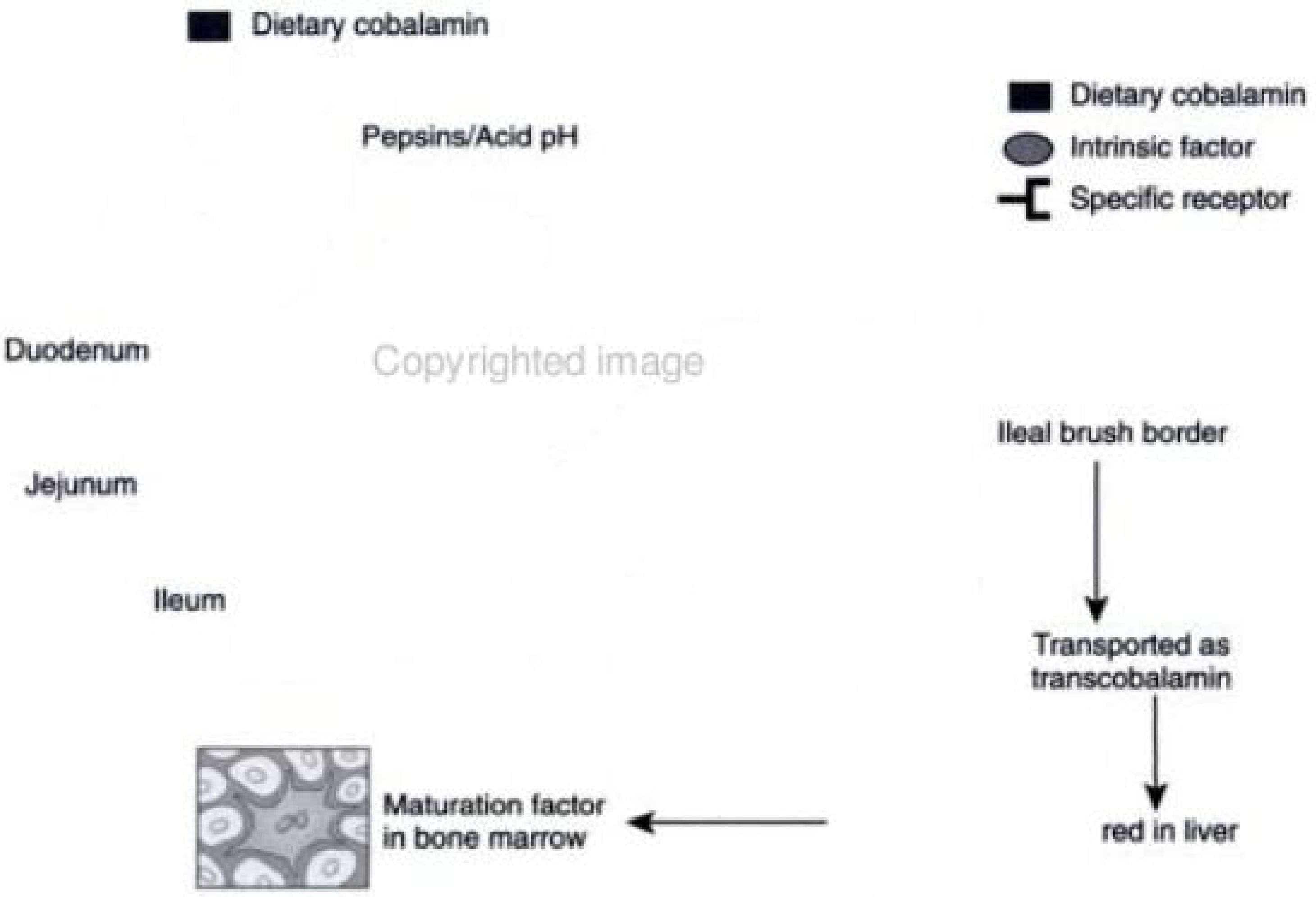

Figure 7–2. The absorption of vitamin B_{12} from the gastrointestinal tract is complicated and depends on the release of intrinsic factor and hydrochloric acid from the stomach. The drug complexes with a receptor. This complex is protected as it passes to the ileum, where it is absorbed by receptor-mediated pinocytosis.

Folic acid is acquired from the diet, although it can also be formed by microbes. Dietary sources include yeast, liver, kidney, and green vegetables. Folic acid is also stored in the liver but not as avidly as is vitamin B_{12}. It undergoes enterohepatic circulation but is destroyed daily by catabolic processes. Daily requirements are high, and serum levels will fall rapidly several days after dietary deficiency. Gastrointestinal absorption of folic acid is not as complex as that of vitamin B_{12}, although it requires protein digestion and the presence of dihydrofolate reductase in the small intestine. Jejunal pathology can result in folate deficiency. The degree of folic acid binding to plasma proteins is not well understood.

Folic acid is available as both a parenteral and an oral (pure or combined product) form. The minimum daily requirement in people is 50 μg/day, but this can increase to 100 to 200 or more in patients with high cell turnover rates (e.g., hemolytic anemia) (Hillman, 1996). In humans, the most popular form of folic acid supplementation is as part of a multivitamin preparation containing 400 to 500 μg of pteroylglutamic acid. In high disease states, one to two 1-mg tablets are consumed. This dose may be the source of the recommended dose for cats and dogs. Compared with commercially available products, the dose recommended for small animals seems excessive, and it is not clear that such a high dose is necessary. There are, however, no apparent significant toxicities associated with therapy.

Indications for therapy are inadequate intake due to administration of several drugs (methotrexate, potentiated sulfonamide antibiotics, some anticonvulsants such as phenytoin), liver diseases, malabsorption, or other chronic debilitating diseases. Folic acid is also available as leucovorin (folinic acid), a congener of folic acid (Hillman, 1996). This drug apparently will serve as a substrate for inhibitors of dihydrofolate reductase such as methotrexate or trimethoprim but will not replace deficient folic acid.

Folinic acid (leucovorin) is a derivative of tetrahydrofolic acid and, as such, does not require the action of dihydrofolate reductase in order to act as a folate by contributing a carbon moiety. In humans, administration of folinic acid increases serum folate activity owing to 5-methyltetrahydrofolate. It is used clinically to circumvent the actions of dihydrofolate reductase (e.g., methotrexate) but is not indicated for treatment of folic acid deficiency.

Hemoglobin Synthesis: Iron

Hemoglobin consists of a heme portion and a globin portion. The heme portion is formed from a pyrrole ring, four of which combine to form a protoporphyrin compound. This in turn combines with iron to form heme. Four hemes combine with the globulin globin to form hemoglobin. Several factors are necessary for hemoglobin formation.

Iron is a component of hemoglobin, myoglobin, and other substances such as those found in cytochrome and electron transport systems (Hillman, 1996; Adams, 1995). About 65% of total body iron is present in hemoglobin, 4% as myoglobin, and 1% in cytochromes and electron transport systems. The remaining 15% to 30% is stored as either ferritin, the soluble form of iron stores, or hemosiderin, the insoluble stores. Oral absorption of iron is slow, complicated, and not well understood (Fig. 7–3). It is available in the diet in either a heme form, which comprises a small percentage of the total but readily absorbed form, or in a nonheme (ferric oxide) form. The nonheme form represents the largest dietary fraction, but its absorption is profoundly affected by dietary factors. Nonheme iron must be converted to the ferrous form for absorption to occur; conversion depends on an acidic environment. Absorption of iron is increased by hydrochloric acid and decreased in situations that decrease acid production in the stomach (e.g., chronic use of antisecretory drugs).

Iron is absorbed primarily from the proximal jejunum,

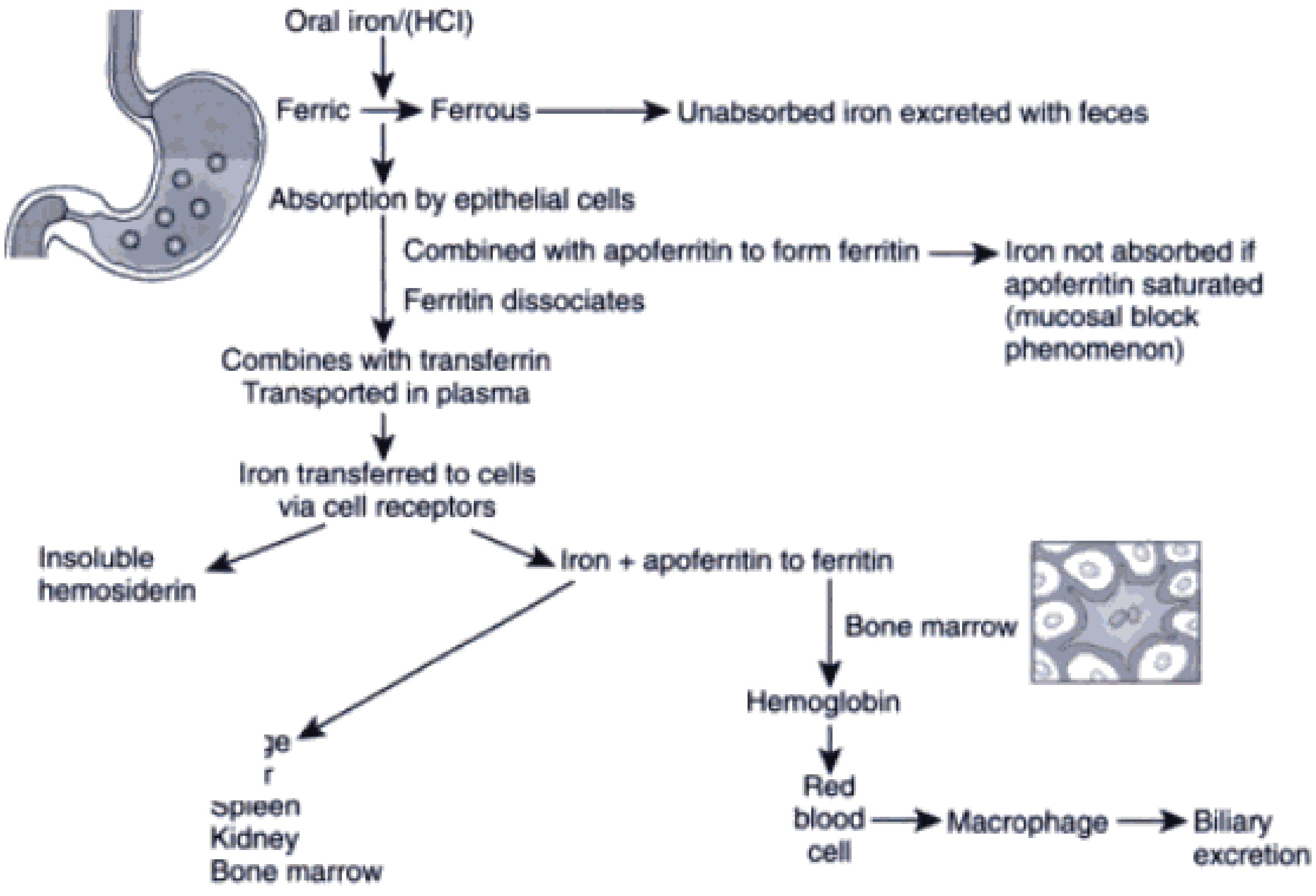
Oral iron/(HCl)
Ferric
Ferrous
Unabsorbed iron excreted with feces
Absorption by epithelial cells
Combined with apoferritin to form ferritin
Iron not absorbed if apoferritin saturated (mucosal block phenomenon)
Ferritin dissociates
Combines with transferrin
Transported in plasma
Iron transferred to cells via cell receptors
Insoluble hemosiderin
Iron + apoferritin to ferritin
Bone marrow
Hemoglobin
Red blood cell
Macrophage
Biliary excretion
ge
r
Spleen
Kidney
Bone marrow

Figure 7–3. Absorption of usable iron from the gastrointestinal tract is maximized in an acid environment. Iron combines with apoferritin in cells to form ferritin, the soluble form of iron. Iron is bound to transferrin in plasma. Saturation of apoferritin leads to saturation of transferrin. Excessive iron is stored as hemosiderin, a nonsoluble form of iron. In the presence of saturation, iron is eliminated in the gastrointestinal tract.

where it immediately combines in the enterocyte to apoferritin to form ferritin. When transferred out of the enterocyte, ferritin dissociates, and iron combines with the globulin transferrin. Iron is transported in the plasma in this form, but the binding is loose so iron can be easily transferred to tissues. Iron is transferred to cells via specific receptors that interact with transferrin, especially in the liver. In cells, iron again combines with apoferritin to become ferritin. Small quantities are also stored as the very insoluble hemosiderin; the quantity of this storage form increases when the total quantity of iron in the body is much more than apoferritin can accommodate. When apoferritin is saturated, transferrin cannot release iron, and it thus becomes close to 100% bound (estimated iron stores).

There is no mechanism for the excretion of iron other than via the gastrointestinal tract. Gastrointestinal tract elimination occurs by (1) exfoliation of enterocytes containing iron, (2) biliary elimination, and (3) (a continuation of 2) elimination in diet of iron not absorbed. Total body iron is regulated by altering the rate of absorption. If all the apoferritin in the enterocyte is combined with iron, the amount of iron in the enterocyte is high, and absorption from the diet is slowed. Absorption is faster if iron stores are depleted. This mechanism has been referred to as the *mucosal block phenomenon*.

Preparations. Iron is available in both oral and parenteral preparations. Oral preparations are prepared as ferrous (bivalent) or ferric (trivalent) salts. Ferrous salts tend to be the treatment of choice for oral supplementation and are dosed according to their iron content (Hillman, 1996). Examples of bivalent ferrous salts include sulfate (20% iron), gluconate (12%), and fumarate (33%). The ferrous bivalent salts are more soluble in the gastric environment and are absorbed three times faster than the trivalent salts. The efficacy of polysaccharide oral iron products approximates that of ferrous products. Slow-release iron products have not been well studied. These products may be continued for several months; toxicities and side effects are dose related.

Parenteral preparations are indicated if oral preparations cannot be tolerated or are not feasible. Iron dextran IM injection generally is the preferred route. Parenteral administration results in a more rapid accumulation of iron stores, which may take months (in people) with oral therapy. Other indications for parenteral therapy include diseases of the gastrointestinal tract that preclude iron absorption or that will exacerbate another disease (e.g., inflammatory bowel disease) or intolerance of oral supplementation (Hillman, 1996). Much of the iron given intramuscularly remains at the site of injection for several months. The remaining iron enters the plasma but must first be phagocytized by reticuloendothelial cells for processing. This may take several months, and evaluation of total body iron may be difficult until all of the iron is processed (Hillman, 1996).

In human patients, iron injection is preceded by a test dose (about 0.5 mL). It is given only in a large muscle mass and is associated with long-term discomfort, local skin discoloration, and a perceived risk of malignant change at the site of injection. Selected iron dextran preparations also can be administered intravenously. Dosing is based on a conversion of body weight (0.66 × weight in kilograms) and on the patient's hemoglobin level compared with the desired hemoglobin level (14.8 g/dL) (Hillman, 1996). After an initial 0.5-mL test dose, the calculated dose is given in 2.0-mL increments each day until completed. Side effects associated with intravenous administration include malaise, fever, arthralgias, urticaria, and generalized lymphadenopathy (Hillman, 1996).

Drug Interactions. Several drugs, including tetracyclines and antacids, and several foods bind to and precipitate iron when given orally. Absorption is enhanced in the presence of ascorbic acid because it reduces ferric iron to its ferrous state and prevents formation of insoluble and unabsorbable iron compounds (Weiss, 1995).

Clinical Use. Indications for iron therapy are limited to treatment or prevention of iron deficiency such as occurs with blood loss or successful therapy with anabolic steroids or recombinant EPO in a patient suffering from chronic anemia. The efficacy of "shotgun" products is questionable. As with any hematinic preparation, provision of these compounds will be ineffective if the nutritional status of the animal is poor. "Shotgun" preparations are products that contain a combination of hematinic agents such as vitamin B_{12}, folic acid, pyridoxine, riboflavin, nicotinic acid, pantothenic acid, thiamine, biotin, ascorbic acid, and vitamin E. The need for inclusion of all of these products is debatable. An exception might be made for ascorbic acid, which enhances oral absorption of iron, and pyridoxine, which is useful in human patients with selected anemias. One human patient with pure red cell aplasia has responded to riboflavin. Occasionally, these products might be considered dangerous because some additives may be sufficiently high to mask clinical signs of other nutrient deficiencies that ultimately may become life threatening (Hillman, 1996).

Erythropoietin

Erythropoietin is an endogenous glycoprotein hormone. The kidney (peritubular cell) is the primary source of endogenous EPO, although the liver produces a small amount in some species. Insufficient oxygen delivery to tissues is the primary stimulus for production and secretion of EPO (Hillman, 1996) (see Fig. 7–1). Prostaglandins appear to increase and nonsteroidal anti-inflammatory drugs appear to decrease EPO production. Human EPO has been isolated and its chemical structure identified, allowing the synthesis of large quantities with recombinant techniques. Although the recombinant human product (rhEPO) is identical to human endogenous EPO, substantial differences exist between the human and animal proteins. Canine EPO also has been isolated and synthesized in recombinant form. Although it is not yet commercially available, it is closely homologous to feline EPO as compared with human EPO and will be preferred to human EPO for treatment in cats.

Mechanism of Action

The influence of rhEPO on RBC production occurs at several steps. It binds to receptors or erythroid precursor cells and initiates changes in intracellular phosphorylation (Hillman, 1996). It stimulates the proliferation and differentiation of erythroid precursors, including BFU–erythroid colony-forming units: erythroid, erythroblasts, and reticulocytes (Hillman, 1996). Recombinant human EPO also stimulates the release of reticulocytes from the bone marrow into the blood, where they subsequently mature (Eschbach and Adamson, 1988, 1989; Faulds and Sorkin, 1989; Schwenk and Halstenson, 1989; Schulman et al., 1986).

Disposition

The disposition of rhEPO has not been well characterized in either humans or animals. In humans, the elimination half-life is about 6 to 9 hours with a very small volume of distribution (0.055 L/kg). As with most endocrine products, plasma half-life may not necessarily reflect biologic half-life (Faulds and Sorkin, 1989; Schulman et al., 1986).

Preparations

Recombinant human EPO is available as epoetin alfa, a formulated product intended for intravenous or subcutaneous injection in humans. It is combined with human albumin.

Adverse Effects

Antibody Formation. Differences in adverse effects reported in humans versus animals should be expected because the protein is foreign in animals. Local and systemic allergic reactions have been reported in animals (Cowgill, 1992, 1995; Cowgill et al., 1994). Cellulitis, fever, arthralgia, and mucocutaneous ulcerations have occurred in 12% of animals treated in a pilot study (Cowgill, 1992, 1995; Cowgill et al., 1994). Signs resolve with drug withdrawal and may not reappear when treatment is resumed. In addition, the rhEPO may stimulate production of antibodies targeted toward rhEPO. Up to 30% or more of dogs and cats treated with rhEPO may develop antibodies. Antibody production, which can occur within 2 weeks, may be accompanied by a progressive decrease in RBCs, hematocrit, and hemoglobin (Cowgill, 1992, 1995; Cowgill et al., 1994). Both exogenous and native EPO may be impaired and ultimately may cause aplastic anemia due to bone marrow failure. Antibodies are indicated by a bone marrow myeloid-to-erythroid cell ratio of less than 8. Discontinuation of rhEPO will result in resolution of antibody formation and—to some degree—the anemia (i.e., that caused by antibodies), but drug therapy cannot be reinstituted (Cowgill, 1995).

Miscellaneous Adverse Effects. Other adverse effects that may require monitoring in patients receiving EPO include systemic hypertension, iron deficiency, hyperkalemia, and polycythemia (Eschbach and Adamson, 1989). Flu-like symptoms occur in some human patients receiving the drug intravenously. Hypertension occurs in many human patients with renal disease as the hematocrit normalizes. Patients who begin the use of rhEPO when in a state of hypertension are likely to experience a further increased in blood pressure. The mechanism of hypertension is not known, but may include increased blood viscosity or peripheral vasoconstriction. Blood pressure increases within as little as 2 weeks of therapy and tends to stabilize by month 4. Increased blood pressure is rare in animals but may occur. Additional therapy may be needed for patients receiving antihypertensive drugs. Other miscellaneous adverse effects of rhEPO in dogs and cats include seizures (rare) and depleted iron stores, particularly in patients with iron deficiency (Cowgill, 1995). In an animal model involving renal ablation, rhEPO hastened the progression of chronic renal disease. The clinical relevance of this finding has not, however, been documented.

Clinical Use

The primary indication for rhEPO in people is anemia of chronic renal disease (Adamson and Eschbach, 1991; Cowgill, 1992; Cowgill et al., 1994; Eschbach and Adamson, 1988, 1989). Most human patients receiving renal dialysis also receive rhEPO. In humans, the drug normalizes the hematocrit, hemoglobin concentration, and RBCs after administration of 15 to 300 U/kg three times weekly. Some human patients have required 500 U/kg. A stair-step approach has been used for nonresponding chronic renal disease in human patients in that the dosage continues to be increased until the desired response is achieved (Eschbach and Adamson, 1989). When the desired response is achieved (a hematocrit of 30% to 40%), a smaller maintenance dose (25 to 100 U/kg three times a week) is given to maintain the hematocrit above 30% (Eschbach and Adamson, 1989). The maintenance dose generally is given subcutaneously, whereas the induction dose is often given intravenously (in human patients). Iron therapy is often begun as rhEPO therapy is begun. Because intravenous iron dextran therapy is more expensive and is associated with anaphylactic therapy, oral iron therapy is preferred (Eschbach and Adamson, 1989; Hillman, 1996). Differences in the gastrointestinal absorption of iron may alter response to rhEPO therapy. Addition of 200 mg of oral iron, however, appears to successfully maintain adequate iron stores in human patients with chronic renal disease receiving rhEPO.

Recombinant human EPO is indicated in dogs or cats with a packed cell volume (PCV) of 20 to 25% or less due to renal disease (Table 7–1). Caution is indicated for patients that are hypertensive before rhEPO therapy. Informed consent should be obtained before use because of the high incidence of antibody formation. Initial treatment should begin at 100 U/kg (or, if a slower increase is acceptable, 50 to 75 U/kg) subcutaneously three times a week until the target hematocrit (37% to 45% in dogs or 30% to 40% in cats) has been reached. The PCV should be measured twice weekly for the first several months of therapy. The frequency of administration can be decreased to twice weekly once the target PCV has been achieved. If the PCV does not increase sufficiently, the dose of rhEPO can be increased in 25- to 50-U/kg increments. The maintenance dose will vary for each patient. A maximum dose has not been established in animals, although weekly doses of 300 to 1050 U/kg have been reported (Cowgill, 1995).

Recombinant human EPO has been used in small animals with chronic anemia (Cowgill, 1992, 1995; Cowgill

Table 7–1. Doses of Drugs Acting on the Blood or Blood-Forming Units

Drug	Dose	Route	Frequency (Days)
Aspirin	0.5 mg/kg (normal dogs)	PO	12
(antithrombotic)	5–10 mg/kg (heartworm)	PO	24
Danazol	5–10 mg/kg (dog)	PO	12
	5 mg/kg (cat)	PO	12
Desmopressin acetate	0.4 µg/kg	SC	24
nasal drop (0.01% spray)	2–4 drops	Nasal mucosa	
	0.1–0.2 mg	PO*	
Erythropoietin (rhEPO)	50–100 U/kg	SC	3/wk†
Fluoxymesterone	0.2–1 mg/kg	PO	1
Folic acid	5 mg (dog)	PO	24
	2.5 mg (cat)	PO	24
Folinic acid	1 mg/kg	PO	24
Heparin‡			
Heartworms	50–70 U/kg	SC	8
	10–100 U/kg	IV (load)§	
	5–10 U/kg	IV infusion	Every hour
Thromboembolism	100–300 U/kg	IV (load)	
	10–50 U/kg	IV infusion	
DIC, mild	5–10 U/kg	SC	8
	75–200 U/kg	SC	8
DIC, severe	300–500 U/kg	SC	8
	750–1000 U/kg	SC	8
Nandrolone decanoate	1–5 mg/kg	IM	7
Nandrolone phenylproprionate	1 mg/kg	IM	7
	25–50 mg/kg (dog)	IM	7–14
	10–20 mg/kg (cat)	IM	7–14
Oxymetholone	1 mg/kg	PO	1
Protamine‖	1–1.5 mg/1 mg heparin	IV	
Stanozolol¶	0.25–3 mg/kg	PO	1
	2–10 mg/kg	IM	7
Testosterone			
Proprionate	2.2 mg/kg	IM	7
Enanthate	4–7 mg/kg	IM	7
Vitamin B_{12}	100–200 µg (dog)	PO, SC	
	50–100 µg (cat)	PO, SC	
Vitamin K_1 (phytonadione)	1 mg/kg (liver disease)	PO	24
	0.125–1.25 mg/kg coumarin or short-acting rodenticides	IM, SC, PO	12
	5 mg/kg (loading dose) (indandione) or long-acting rodenticides	SC, PO	—
	2.5 mg/kg	SC, PO	24
Warfarin†	0.1–0.2 mg/kg (dog)	PO	24
	0.5 mg/kg (cat)	PO	24

Abbreviations: IM, intramuscular; IV, intravenous; PO, oral; SC, subcutaneous.

*Dose for the oral preparation has not been substantiated. As of this writing, the acetate preparation is no longer available in the United States.

†Monitor packed cell volume twice weekly for the first several months and modify dose as appropriate.

‡Adjust dose by monitoring activated partial thromboplastin time to 1.5 to 2.5 times baseline.

§Or in blood products, incubated for 30 minutes before administration.

‖No more than 50 mg/10 min. Dose is reduced if time lapses between heparin overdose and protamine administration.

¶Approved for use in dogs and cats.

et al., 1994). When administered in uremic animals with chronic renal disease, the hematocrit of most patients normalizes within 3 to 4 weeks of therapy, and the clinical well-being of patients improves. Response to therapy is indicted by reticulocytosis and an increase in hematocrit of 0.5% to 1.0% each day. Hypokalemia associated with uremia in cats should also resolve, in part because of improved appetite (Cowgill, 1995). White blood cells and platelets do not seem to be affected.

Erythropoietin is indicated for treatment of anemias associated with decreased levels of endogenous EPO. The drug has, however, proved useful in some cases of nonrenal disease anemia in humans (Garton et al., 1995). The most common nonrenal use in people has been in anticipation of autologous blood transfusion. The drug has also been used to treat sickle cell anemia and, more recently, multiple myeloma in people (Garton et al., 1995).

Therapeutic Failure

The most likely reason for a patient to not respond to rhEPO is inappropriate therapy. If the anemia is not associated with chronic renal disease, rhEPO therapy may be ineffective if endogenous rhEPO concentrations are maximally increased. Several reasons can account for failure in a patient with low endogenous rhEPO. The dosage may be insufficient. Failure of an anemic animal to respond to rhEPO may indicate the development of antibodies directed toward rhEPO (Cowgill, 1995). Failure to respond to rhEPO should stimulate a search for anemia not related to renal disease (e.g., inflammatory disease, neoplasia, hemolytic disease) or antibody formation. Iron supplementation will be necessary for most patients (Cowgill, 1995). Chronic inflammatory disease decreases response to rhEPO, as do myelophthistic diseases that replace bone marrow with fibrous tissue. Alternatively, anemia may persist because patient nutrition is not sufficient to support increased EPO. Iron deficiency before or during therapy will blunt the response to rhEPO; iron supplementation should be implemented. Oral absorption of iron may not occur until serum ferritin is below 30 to 50 ng/mL (human patients). Erythropoiesis improves, however, even in human patients whose transferrin saturation is above that diagnostic of iron deficiency (16%) (Wingard et al., 1995).

Granulopoietin and Related Products

At least six growth factors influence granulopoiesis (Hillman, 1996). Formation of both granulocytes and macrophages from multipotential stem cells is stimulated by stem cell factor, a glycoprotein produced by bone marrow stromal cells; interleukin-1 (IL-1) and interleukin-6 (IL-6), inflammatory cytokines that mediate many of the systemic manifestations of acute inflammation; interleukin-3 (IL-3). GM-CSF, along with G-CSF, is produced by a variety of tissues in response to cytokines such as IL-1, tumor necrosis factor, and endotoxin (Weiss, 1995; Hillman, 1996). Supplementation with exogenous factors stimulates the proliferation of various cell types, with the type affected depending on the factor or combination of factors. Interleukin-3 increases both platelets and granulocytes, and GM-CSF administered by itself stimulates granulocyte and macrophage proliferation. When given in combination with IL-3, however, GM-CSF stimulates thrombopoiesis, and when combined with EPO and IL-3, erythropoiesis is stimulated (Tyrrell et al.,).

As with EPO, recombinant products have been developed for therapeutic stimulation of granulopoiesis. Both recombinant canine (rcGSF) and recombinant feline (rfGSF) G-CSF have been cloned, but neither is commercially available at this time. Feline GSF has much closer homology with rcGSF than with rhGSF and, as such, is the preferred product. Despite their lack of availability, the factors are increasingly being studied for treatment of neutrophil disorders in dogs and cats (Kruth, 1995; Weiss, 1995).

In normal dogs, G-CSF (5 μg/kg per day) will increase neutrophil counts over fourfold within 24 hours, reaching a maximum of approximately 72,000/mL by 19 days, with counts returning to normal within 5 days after discontinuation of therapy (Kruth, 1995). In dogs afflicted with cyclic neutropenia, rcGSF (2.5 μg/kg every 12 hours) prevents neutropenia and associated clinical signs, although cycling of neutrophils is not prevented. Chemotherapy-induced neutropenia (induced by mitoxantrone) was minimized in dogs receiving rcGSF for 20 days. Studies in normal cats receiving rcCSF reveal an approximately threefold increase in neutrophil count that persists until the drug is discontinued. No adverse effects occur (Kruth, 1995).

Other compounds have been studied for their effect on granulopoiesis. An extract of *Serratia marcescens* activates interferon-α and interferon-γ as well as IL-1, IL-6, and GM-CSF and induces myeloproliferation either directly or through release of other cytokines (Kruth, 1995).

Anabolic or Androgenic Steroids

Chemistry

Anabolic steroids are synthetic compounds structurally related to testosterone. They have protein-anabolic activity similar to that of testosterone but minimal androgenic effects (i.e., minimal masculinization) (Dennis, 1990; Bagatelle and Brenner, 1996). Testosterone is the sole endogenous androgen in most mammals. Its androgenic effects and rapid elimination have led to the manufacture of synthetic compounds. Chemical manipulations that have produced clinically useful anabolic steroids include (Fig. 7–4) (1) alkylation (addition of a methyl $[CH_3]$ group) at the 17α position (e.g., stanozolol), which impairs hepatic metabolism, thus prolonging elimination half-life; (2) esterification of the 17β hydroxyl group (e.g., Deca-Durabolin) such that absorption from parenteral sites is prolonged; and (3) modification of the steroidal ring structure. The sequelae of changes in the steroidal structure vary with the modification and include prolonged absorption or elimination.

Mechanism of Action

The mechanism of hematinic action of anabolic steroids on the cellular level is typical of the steroidal compounds (Molinari, 1982; Bagatelle and Brenner, 1996; Majerus et al., 1996; Wilson, 1996). Anabolic steroids enter the RBC, where they enhance glycolysis and the formation of steroidal 17-keto-metabolites. These metabolites are delivered to tissues, including the bone marrow, where they interact with a cytosolic receptor in the appropriate cell and are transferred to the cell nucleus. In the nucleus, they induce the formation of RNA and synthesis of an effector protein that brings about the pharmacologic effect.

The sequelae of steroid-induced nuclear transcription are manifold (Majerus et al., 1996; Wilson, 1996). The proposed sequelae on RBC formation include (1) stimulation of EPO production via EPO-stimulating factor, (2) differentiation of stem cells into EPO-stimulating factor-sensitive cells (e.g., hemocytoblasts), and (3) direct stimulation of erythroid-progenitor cells. Anabolic steroids also increase intracellular concentrations of 2,3-bisphosphoglycerate in erythrocytes; oxygen release into tissues is subsequently increased.

Efficacy of the anabolic steroids on the RBC mass depends on the presence of supportive materials (Majerus et al., 1996; Wilson, 1996). This includes adequate concentrations of androgen dehydrogenase in the RBC, adequate EPO concentrations, and sufficient bone marrow cellularity. Thus, the effectiveness of anabolic steroids in treating anemia may be limited depending on the cause (i.e., renal disease accompanied by low EPO levels). Administration of high doses of these steroids may cause a negative feedback inhibition.

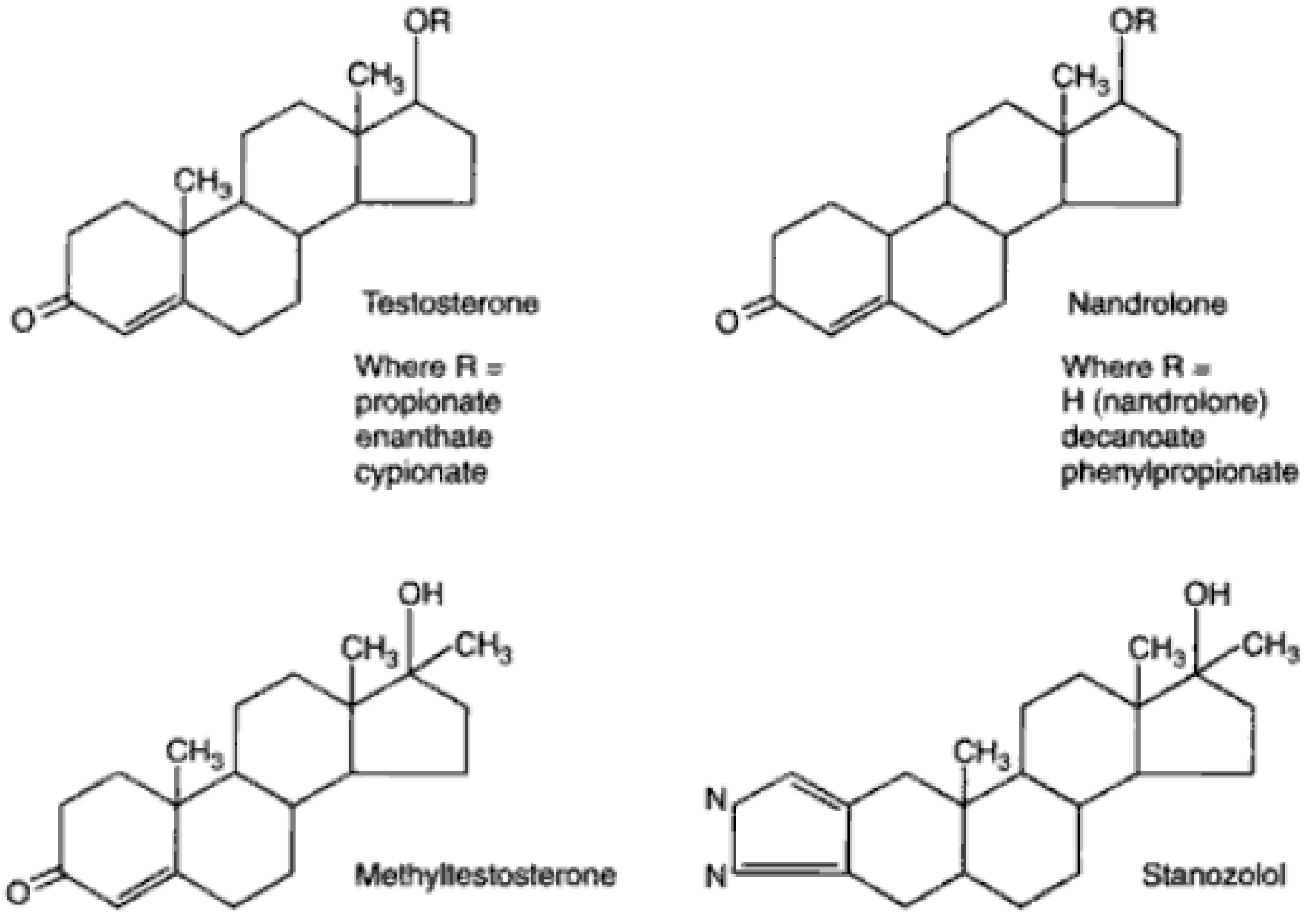

Figure 7–4. Methylated anabolic steroids include methyltestosterone, oxandrolone, and stanozolol. Nandrolone is a nonmethylated anabolic steroid. Nonmethylated products tend to be less efficacious but less hepatotoxic.

Pharmacologic Effects

The difference in the pharmacologic effects of these drugs among the various tissues and, specifically, whether an androgenic versus an anabolic effect will predominate cannot be attributed to differences in target tissue receptor structure because there appears to be only one androgen receptor type. Differences in response may be concentration dependent (e.g., reproductive tissues requiring higher concentrations than nonreproductive tissues). Alternatively, differences in response may reflect conversion of the drug by target tissues to an active metabolite that subsequently causes the pharmacologic effect (Majerus et al., 1996; Wilson, 1996).

In the presence of continued administration, anabolic steroids initiate and maintain a positive nitrogen balance, although the response is short-lived in intact males (Bagatelle and Brenner, 1996; Majerus et al., 1996; Wilson, 1996). They antagonize glucocorticoid-induced protein catabolism by competitively inhibiting glucocorticoid binding to glucocorticoid receptors. Although anabolic steroids appear to vary in their ability to antagonize the effects of glucocorticoids, protein anabolism may be induced in patients experiencing glucocorticoid-induced protein catabolism. Anabolic steroids also reduce urinary excretion of nitrogen, sodium, potassium, chloride, and calcium.

As part of their anabolic activity, these compounds increase the circulating RBC mass (and possibly granulocytic mass). Red blood cell indices, hemoglobin, and hematocrit increase in various types of anemia. White blood cell mass may increase in cases of pancytopenia, although white blood cell response takes longer than the RBC response. Response by thrombocytes is slower and less predictable (Bagatelle and Brenner, 1996; Majerus et al., 1996; Wilson, 1996).

Pharmacokinetics

The absorption and disposition of these anabolic steroids depends on the type of preparation, the presence of specific receptors, and the species to which it is administered (Bagatelle and Brenner, 1996; Majerus et al., 1996; Wilson, 1996). Most anabolic steroids depend on hepatic metabolism for elimination.

Preparations

Anabolic steroids can be divided into two categories depend on the presence or absence of an alkyl (CH_3) group at the 17-carbon position (see Fig. 7–4) (Majerus et al., 1996; Wilson, 1996). Oral and parenteral preparations are available, with the alkylated products being better absorbed orally. Oil-based parenteral preparations are intended for slow release. Examples of alkylated anabolic steroids include methyltestosterone, fluoxymesterone (oral), oxymetholone (oral), stanozolol (oral and parenteral), methandrostenolone, ethylestrenol, and norethandrolone (see Table 7–1). Examples of nonalkylated anabolic steroids include testosterone, methenolone, dromostanolone, and nandrolone (parenteral).

Toxicity Versus Efficacy

Hepatotoxicity is the most common serious adverse effect associated with androgenic or anabolic steroids (Majerus et al., 1996; Wilson, 1996). Toxicity ranges from mild increases in clinical laboratory tests to hepatocellular carcinoma (in humans). Drugs alkylated at the 17-carbon position are more likely to cause hepatotoxicity. Although the mechanism is not known, the drugs or their metabolites may be carcinogenic or may increase the metabolism of other drugs to carcinogenic or hepatotoxic compounds. Cholestatic liver damage occurs early and can be significant but is apparently reversible if the drug is discontinued before irreversible hepatic lesions develop.

Masculinization is a major undesirable (or desirable) side effect of anabolic steroids in humans (Bagatelle and Brenner, 1996; Majerus et al., 1996; Wilson, 1996). Virilization can occur but is seldom objectionable in dogs or cats. In dogs and cats, anabolic steroids increase libido in males, interfere with the female reproductive cycle, and cause masculinization of fetuses if administered during pregnancy. Other undesirable consequences of anabolic steroid therapy in dogs include hyperplasia of the perineal glands and stimulation of androgen-dependent tumors, such as anal carcinomas and prostatic carcinomas. In humans, edema due to water retention occurs (Bagatelle and Brenner, 1996; Majerus et al., 1996; Wilson, 1996).

Clinical Indications

Human recombinant EPO has largely replaced anabolic steroids in the treatment of chronic anemias, particularly those associated with renal disease. Anabolic steroids are, however, indicated for treatment of chronic, nonregenerative anemias that fail to respond to EPO; for animals that react adversely to EPO; or for hematopoietic diseases that are not typically associated with decreased concentrations of EPO (Majerus et al., 1996; Wilson, 1996). Fifty percent or more of human patients with aplastic anemias who have failed conventional therapy of anemia have responded to anabolic steroids (Majerus et al., 1996; Wilson, 1996). Anabolic steroids have been used in conjunction with anticancer chemotherapeutic drugs in order to protect bone marrow production of RBCs, thus allowing longer and perhaps more toxic chemotherapy (Bagatelle and Brenner, 1996; Majerus et al., 1996; Wilson, 1996). Anabolic steroids presumably help decrease the catabolic effects of cancer. Treatment several weeks before cancer chemotherapy may enhance response to anabolic steroids. Use of anabolic steroids for cancer has not been established in dogs and cats.

Hematopoietic response to anabolic therapy is variable, and the time to clinical improvement is long, frequently 3 or more months. Cellularity of the bone marrow appears to determine rate of response to anabolic steroids. Cessation of therapy may result in recurrence of the underlying diseases. Among the anabolic steroids, nandrolone decanoate has the greatest hematopoietic effect (Majerus et al., 1996; Wilson, 1996). Leukocyte and thrombocyte counts may also increase after therapy with anabolic steroids, although these effects are slower in onset and less likely, particularly for thrombocytes. Danazol is the anabolic steroid of choice in the treatment of thrombocytopenia, especially that which is immune mediated. Beneficial effects probably include impaired clearing of IgG-labeled platelets and decreased antibody formation. Response to therapy may take several months, and relapse may occur when danazol therapy is discontinued. Anabolic steroids and, in particular, danazol, have been used with some benefit for patients with hemolytic anemia. Benefits include not only expansion of the RBC mass but also impaired complement activation and binding to RBCs. Human patients suffering from anemia due to renal disease respond to continuous administration of anabolic steroids. Red blood cell indices improve as well as appetite, muscle mass, and strength.

In general, the following approaches should be used with anabolic steroids in dogs and cats (see Table 7–1). State restrictions regarding the use of these drugs should

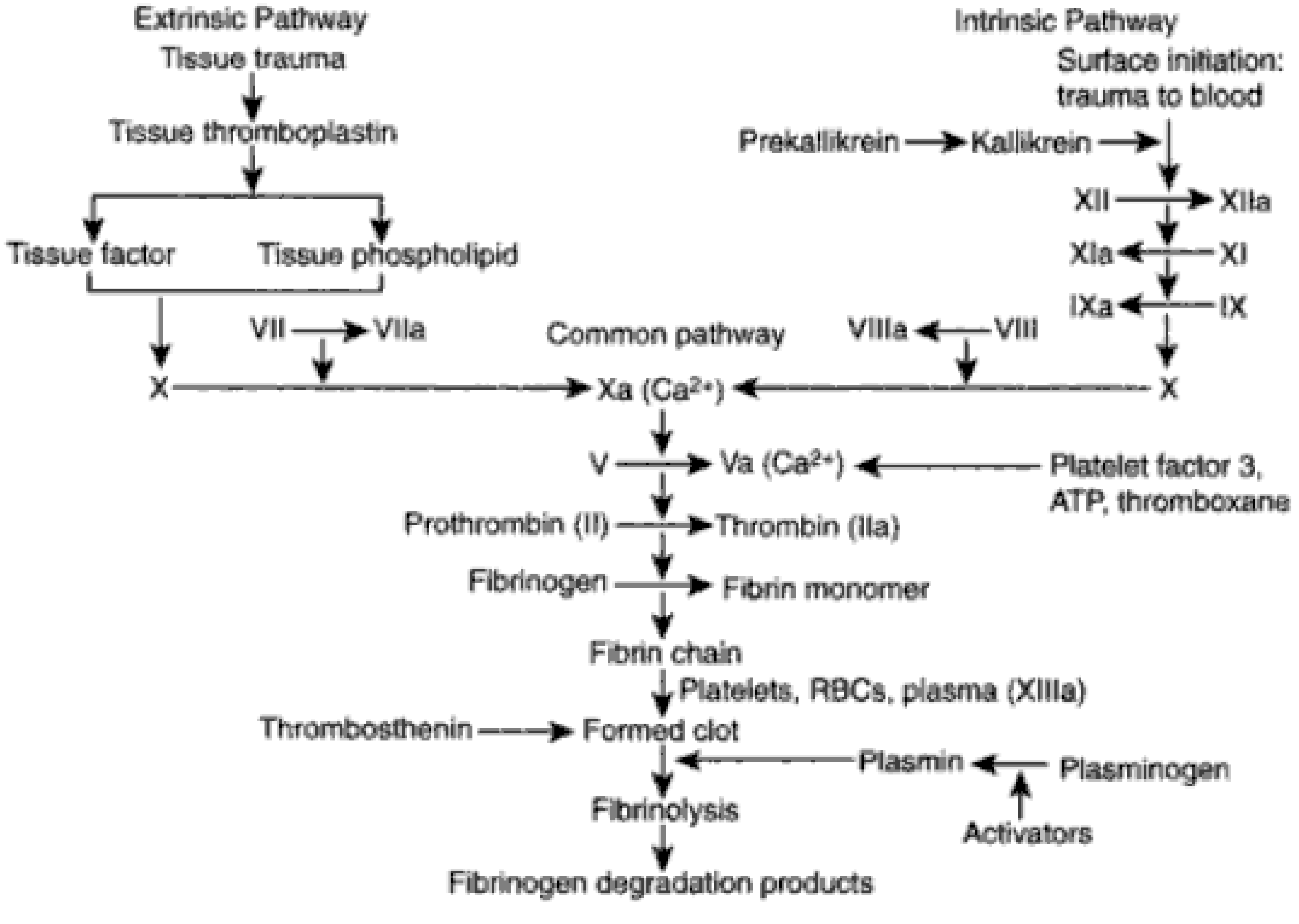

Figure 7–5. Hemostasis occurs in several phases: vascular and platelet; coagulation; and fibrinolysis. Each phase must remain in a balanced equilibrium to maintain a normal state of hemostasis. Endogenous procoagulants and anticoagulants function in each phase. The vascular and platelet phase is composed of vascular wall contraction and platelet adherence. Damage to the vessel exposes subendothelial collagen, which stimulates platelet adherence, which, in turn, depends on von Willebrand factor. Activation of the coagulation phase relies on a complex series of interdependent events. Injury results in activation of procoagulant substances in a cascade manner. Activation (designated by a lower case a, e.g., Xa) generally occurs as a result of proteolysis of a small molecule from the inactive factor. The major events in the coagulation cascade include formation of thromboplastin as a result of tissue trauma (designated as intrinsic if the blood is damaged and extrinsic if the vascular structures are damaged); transformation of prothrombin to thrombin; and rapid conversion of fibrinogen into fibrin. Calcium is involved as a factor at several steps. The fibrinolytic phase is initiated by the conversion of plasminogen to plasmin, which degrades fibrin.

be observed. Nandrolone decanoate is the drug of choice except in cases of thrombocytopenia, for which danazol is the drug of choice. Several months of therapy may be necessary before a clinical response is observed. The dose should be decreased once the maximum therapeutic effect occurs. Relapse of disease may occur once the drug is discontinued, and hepatotoxicity is a potential contraindication for use of these drugs.

DRUGS ACTING ON COAGULATION OR CLOTTING

Hemostatic Drugs

Hemostatic drugs are used to prevent or attenuate bleeding. They can be administered either as topical agents or systemically. In general, topical agents either act as a factor in the coagulation cascade or stimulate some aspect of the coagulation cascade (Fig. 7–5).

Topical

Lyophilized concentrates of one or more clotting factors are available as topical preparations. These preparations usually provide an artificial factor or structural matrix that facilitates clotting (Fig. 7–6). An intact hemostatic mechanism is necessary for their efficacy. These are absorbable products and are indicated for capillary oozing from small, superficial vessels. Examples of concentrated factors include thromboplastin (prothrombin is converted to thrombin, used locally in surgery), thrombin (converts fibrinogen to fibrin; available as powder, solution, or sponge), and fibrinogen. Examples of artificial matrices include absorbable gelatin sponge and oxidized cellulose (treated surgical gauze that promotes clotting) (Fig. 7–7).

Astringents act locally by precipitating proteins. These agents do not penetrate tissues and thus are restricted to surface cells. They can be damaging to surrounding tissues. Examples include ferric sulfate, silver nitrate (e.g., sticks; Fig. 7–8), and combinations that include tannic acid (e.g., STA).

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Figure 7–6. Oxidized cellulose (Surgicel shown here) provides a matrix for clotting.

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Figure 7–7. Gelfoam provides an artificial structural matrix that initiates the clotting process.

Epinephrine and norepinephrine are hemostatic drugs by virtue of their vasoconstrictive effects. They may be included in topical medications to decrease blood flow to the tissues.

Systemic

Fresh blood or blood components are hemostatic drugs only in states of (coagulation) factor deficiency. Examples

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Figure 7–8. Products that contain silver nitrate (shown here), tannic acid, or salicylic acid precipitate proteins and cause coagulation by destroying tissue. Their use is limited to small, topical lesions.

include plasma (contains electrolytes, albumin, and some coagulation factors), fresh frozen plasma (plasma in which factors V and VII are stable), cryoprecipitate, and platelet-rich plasma (see Chapter 6).

Vitamin K. Vitamin K is a hemostatic drug only in instances of vitamin K deficiency. It is necessary for hepatic synthesis of coagulation factors II, VII, IX, and X (Fig. 7–9). Several forms of vitamin K are available for therapeutic use. Vitamin K_1 (phytonadione), the plant form, can be given parenterally and orally. It is more effective, and is effective at a faster rate, than other analogues. Anaphylactic reactions have, however, been reported with intravenous administration and should be particularly anticipated in preparations containing polysorbate 80, a known histamine releaser in dogs. The drug can also be given intramuscularly. The effects of vitamin K_1 occur within 1 hour of administration (Adams, 1995; Sisson and Thomas, 1995), although several hours are needed to resolve bleeding tendencies due to coagulation protein deficiencies.

Vitamin K_2 (menaquinone) is the natural animal and microbial form of vitamin K. Vitamin K_3 (menadione) is the synthetic form and must be metabolized to the active state. Vitamin K_3 usually is absorbed too slowly to be used effectively in acute conditions, but it can be used for chronic therapy once the acute crisis has been resolved. In states of hypocoagulation, vitamin K_1 is the preferred form administered either subcutaneously or orally (3 mg/kg subcutaneously in multiple sites followed by 1 mg/kg every 24 hours parenterally or orally) (Greene and Thomas, 1995). Fat will enhance the oral absorption of vitamin K.

The most common use of vitamin K is treatment of rodenticide toxicity (see later discussion of anticoagulants). Duration of treatment for rodenticide poisoning will vary according to the toxicant. Toxicities from rodenticides containing coumarin or warfarin should be treated for 4 to 6 days; intoxication with diphacinone or brodifacoum requires treatment for at least 14 days (Greene and Thomas, 1995). For toxicity with longer acting rodenticides (i.e., indandiones), the dose of vitamin K is often reduced for subsequent weeks (Greene and Thomas, 1995): 0.5 mg/kg, week 2; 0.25 mg/kg, weeks 3 and 4. Prothrombin time should be monitored for 2 days after vitamin K is discontinued to detect residual rodenticide toxicity. Screening tests should remain normal for 3 to 4 days after therapy has been discontinued.

Protamine Sulfate. Protamine sulfate is a low molecular weight, positively charged drug that binds to heparin, forming a salt and neutralizing its anticoagulant effects. It is used as a procoagulant only in instances of heparin overdosing. Protamine should be used cautiously because it also has anticoagulant activity, probably by impairing thrombin and fibrinogen. It is difficult to dose accurately because the dose is based on the amount of heparin to be antagonized (1 to 1.5 mg protamine for each 1 mg of heparin). In addition, the dose decreases as time elapses after heparin was administered (Adams, 1995b). No more than 50 mg should be given in a 10-minute period.

Desmopressin. Desmopressin (deamine 8-D-arginine vasopressin), a synthetic analogue of vasopressin used to treat central diabetes insipidus, also transiently elevates serum concentrations of von Willebrand factor. The maximum response occurs 1 to 2 hours after treatment. The increase is sufficient to provide improved coagulation activity in animals suffering from von Willebrand disease that undergo surgery (Greene and Thomas, 1995). Desmopressin causes the release of preformed von Willebrand

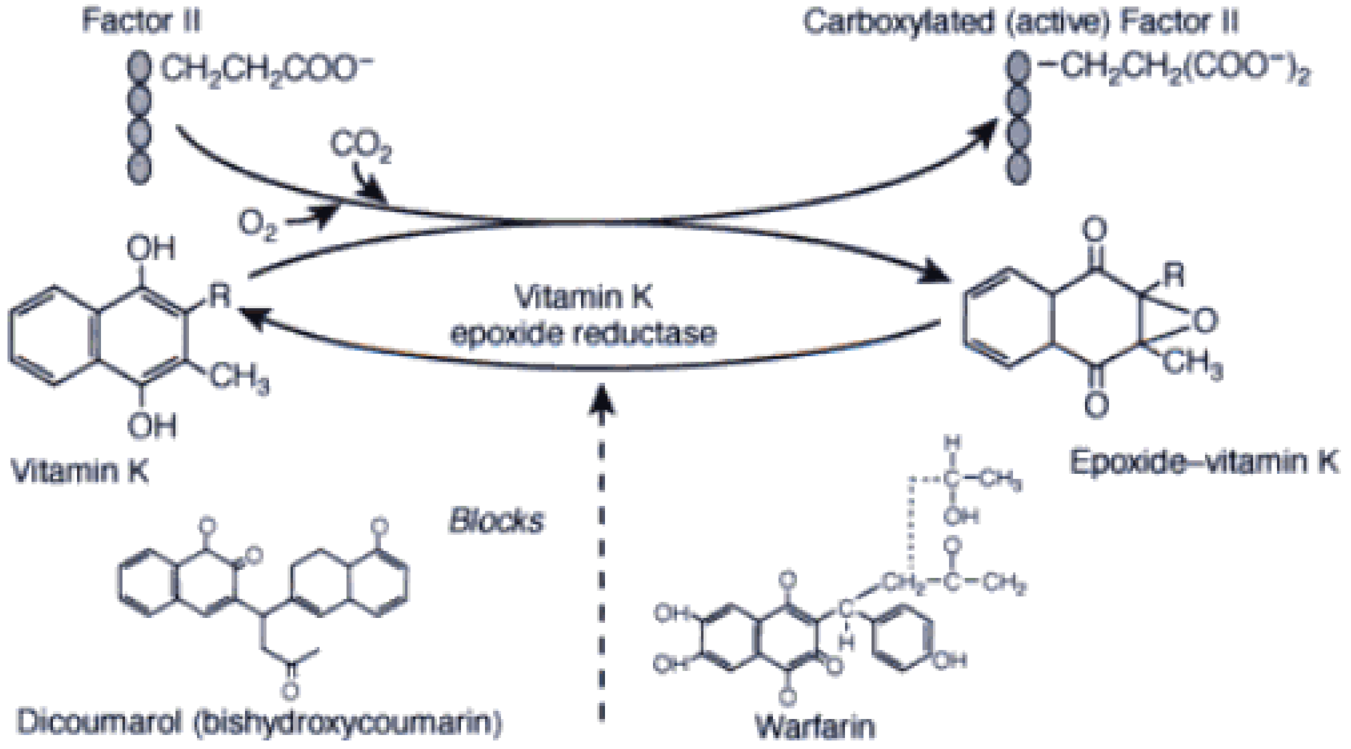

Figure 7–9. Vitamin K catalyzes the carboxylation of factors II, VII, IX, and X. As part of the reaction, the oxidized vitamin must be reduced in order to continue activation of coagulation factors. Coumarin derivatives block the reduction of vitamin K, rendering it incapable of activating coagulation factors.

factor from endothelial cells and macrophages. Repetitive administration results in depletion of the storage pools and loss of procoagulant effect (Greene and Thomas, 1995).

Fibrinolysin Inhibitors. Fibrinolysin inhibitors prevent the activity of plasmin (fibrinolysin) and therefore promote the persistence of clots (see Fig. 7–5). Aminocaproic acid is one of the few examples. Its therapeutic use is limited to treatment after an overdose of a fibrinolytic agent.

Antihemostatic Drugs

Drugs used to limit the formation of thrombi include anticoagulants, thrombolytics, and antithrombotics.

Anticoagulants

Anticoagulants interfere either directly or indirectly with the clotting cascade (see Fig. 7–6). Several in vitro anticoagulants are used for blood collection intended for transfusion therapy and should be considered as drugs. Examples include citrate phosphate dextrose, acid citrate dextrose, sodium citrate, and heparin. All except heparin (see later) act by effectively removing Ca^{2+} from the cascade system (see Chapter 6). In vivo anticoagulants include heparin and the vitamin K antagonists.

Heparin

Heparin is a heterogeneous mixture of sulfated (anionic) polysulfated glycosaminoglycans (PGAG) (Fig. 7–10). Glycosaminoglycans are a family of structurally diverse and distinct polyanionic complex carbohydrates. Included in this group are heparin, heparan sulfate, chondroitin 4-sulfate, chondroitin 6-sulfate, dermatan sulfate, and hyaluronic acid. Each is composed of repeating polysaccharides consisting of an amino sugar and uronic acid. Endogenous synthesis results in multiple compounds that vary in the lengths of carbohydrate chains. Heparin and heparan sulfate are the most complex members of this class of compounds and are characterized by the greatest biologic diversity (Tyrrell et al., 1995).

Heparin was named because of its initial discovery in high concentrations in the liver. It is stored in mast cells, along with other PGAGs such as chondroitin and dermatan sulfate. Heparin is also stored in the body in basophils and, to a lesser extent, in vascular endothelium. Tissues with high concentrations of mast cells serve as a source of heparin. Commercially available heparin is prepared from porcine intestinal mucosa and bovine lung. Heparin is often located attached to serine residues of core proteins (e.g., coagulation factors). Heparan sulfate proteoglycans are more diverse in location. They are an integral part of stromal matrices, basement membranes, and almost all cell surfaces where they provide cohesion between vessels and vascular stroma (Tyrrell et al., 1995).

Heparin is composed of alternating sequences of sulfoaminoglycosamine and uronic acid units, smaller amounts of *N*-acetylglucosamine (see Fig. 7–10), and a unique pentasaccharide sequence that binds to antithrombin III (ATIII) and serves as the active site of the molecule. The number of active sites is variable. The molecular weight of heparin varies from 1800 to 30,000 daltons. Smaller molecules (1800 to 5500 daltons) have a very high affinity for ATIII and comprise less than 5% of endogenous heparin. They are variably referred to as *low-molecular-weight polymers* or *fractions*. Low-molecular-weight (LMW) heparin can be filtered and separated from higher molecular weight heparin. Preparations of heparin also contain contaminants such as dermatan sulfate. Some of these compounds also have anticoagulant activity, albeit less than heparin (Freedman, 1992).

Mechanism of Action. Heparin and heparan sulfate proteoglycan interact with cell surface-binding proteins (which are not necessarily true receptors) and are internalized into cells by receptor-mediated endocytosis. Heparin interacts with many proteins, probably by electrostatic forces between the polyionic groups of the glycosaminoglycan and the cationic groups of proteins. Example proteins include proinflammatory chemokines, growth factor, extracellular matrix proteins, and leukocyte proteins. Interaction between heparin and proteins is best exemplified by the anticoagulant actions of heparin (Tyrrell et al., 1995).

The mechanism of action of heparin as an anticoagulant is indirect. It facilitates the endogenous serine proteinase inhibitor ATIII by binding to aminolysyl residues and heparin cofactor II (HCII) (Fig. 7–11). These anticoagulants normally form stable complexes and subsequently inhibit clotting factors (thrombin being the most important). By binding to the anticoagulants, heparin changes their conformation, exposing active sites so that the velocity, but not magnitude, of interaction between the anticoagulants and clotting factors is increased. The rate of interaction can increase 10,000-fold in the presence of heparin. Heparin is not destroyed but is released to interact with other molecules, leaving behind an inactive ATIII-serum protease

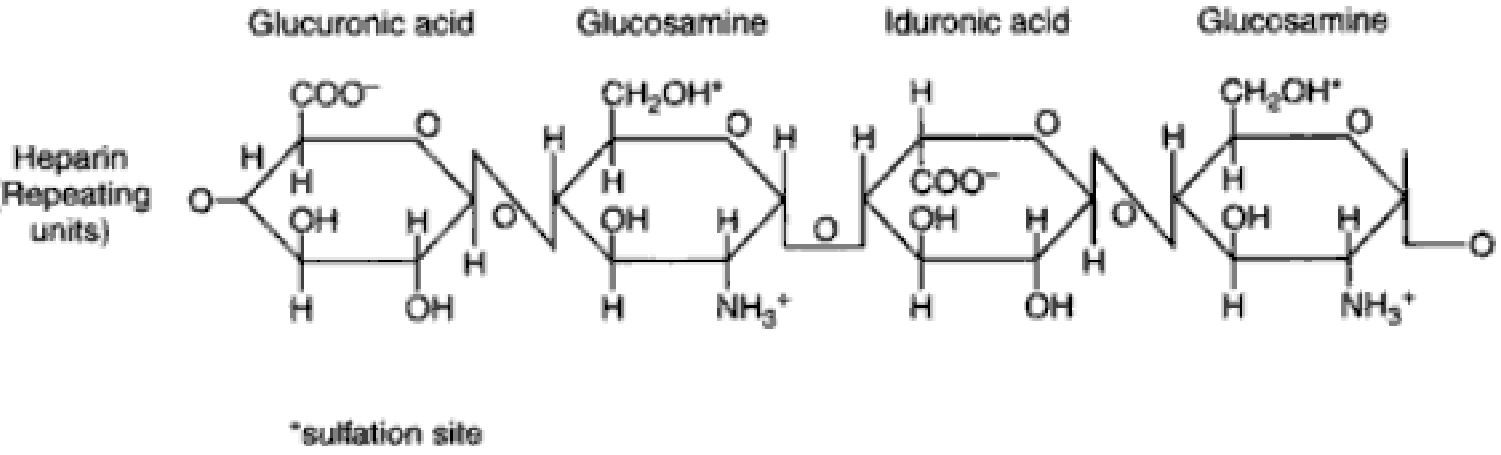

Figure 7–10. Heparin is a heterogeneous mixture of sulfated, anionic, and polysulfated glycosaminoglycans. The subunits include uronic acid, sulfonaminoglycosamine, *N*-acetylglucosamine, and a pentasaccharide sequence.

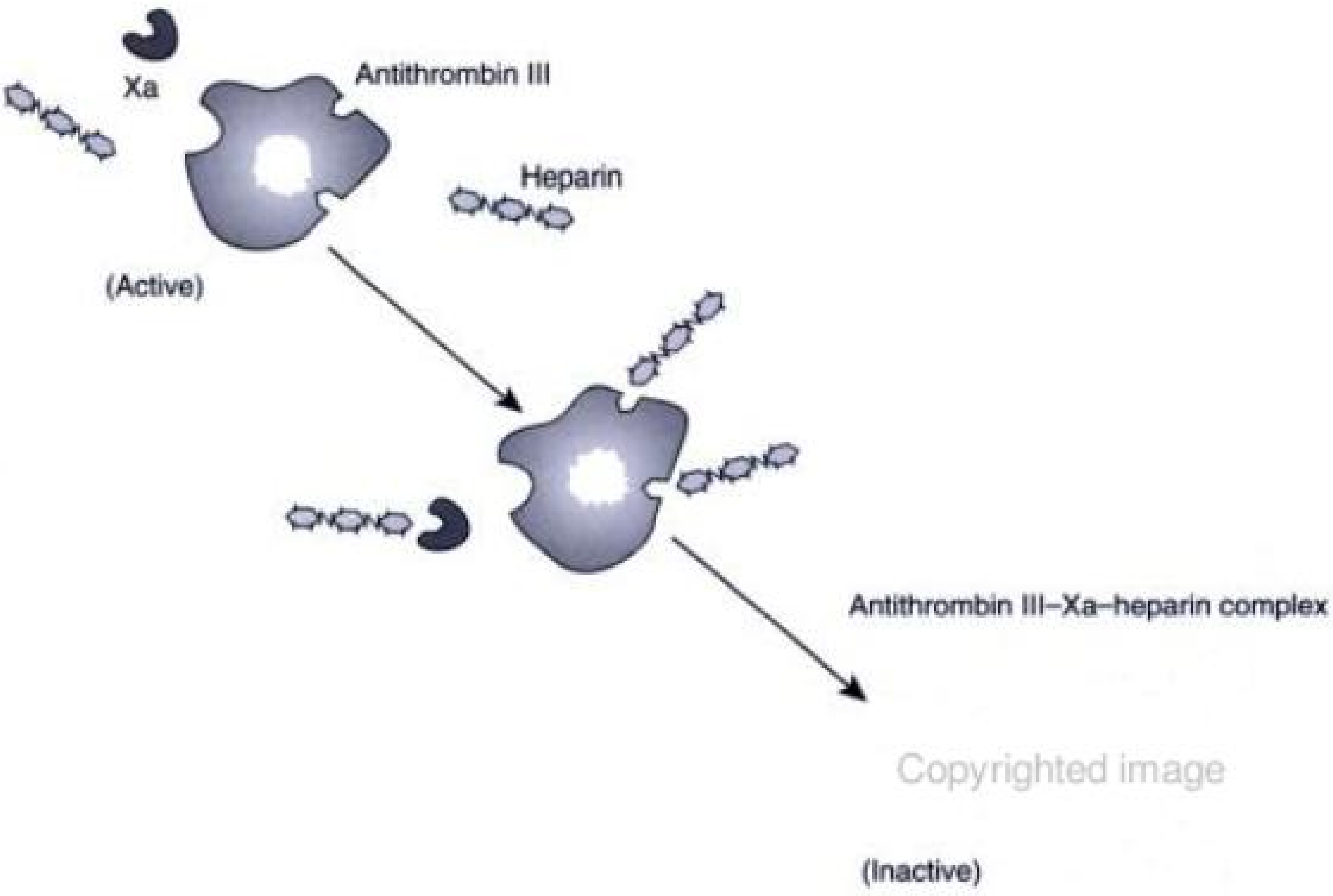

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Figure 7–11. The pentasaccharide sequence of heparin interacts with the amino residues of antithrombin III, changing the conformation of antithrombin II and its ability to interact with factors IXa, XIa, XIIa, and, in particular, II and Xa. Heparin may directly interfere with factor X.

complex. Whereas ATIII inhibits factors IX, I, XI, and XII and kallikrein, the HCII complex interacts only with thrombin. Heparin greatly enhances inhibition of factors IIa and Xa but also inhibits factors IXa and XIa. Low-molecular-weight heparin fractions are more potent anticoagulants than are high-molecular-weight (HMW) fractions (Freedman, 1992). However, the HMW heparins may be more effective anticoagulants because their large structure facilitates binding of both ATIII and thrombin simultaneously (Adams, 1995b).

Heparins have an antiplatelet effect due to a high affinity for platelet factor IV. Most heparin preparations also inhibit platelet aggregation and negate the effects of platelet-derived growth factor on vascular smooth muscle. Thus, heparins are also referred to as *platelet-active anticoagulants*. Heparins also bind to vascular endothelium, causing release of two other endogenous PGAGs and altering vascular endothelial permeability (Freedman, 1992).

Heparin has other effects not related to its anticoagulant activity. In human patients, its use is being considered for prevention of atherosclerosis and for accelerated formation of collateral circulation in the presence of thrombosis (angiogenesis) (Folkman and Shing, 1992; Freedman, 1992). Heparin can inhibit or modulate selected targets of an allergic inflammatory response, including neutrophils and T cells. Derivatives of low anticoagulant activity block superoxide anion generation, probably by interacting with superoxide dismutase. Heparin appears to block mast cell degranulation by altering intracellular calcium release through blockade of inositol 1,4,5-triphosphate receptors. Heparins appear to decrease leukocyte adherence to vascular endothelium and facilitate leukocyte migration along a chemoattractant gradient to sites of inflammation (Tyrrell et al., 1995).

Heparin also appears able to influence tumor cell metastasis. Tumor cell invasion from the vasculature probably involves host degradative enzymes. Among the enzymes are heparinases, which target heparin and heparan sulfate. Exogenous heparin inhibits the hydrolysis of heparan sulfate. Heparins with low anticoagulant activity have reduced the metastasis of several tumor types in various experimental models (Tyrrell et al., 1995).

Smooth muscle cell proliferation such as that which accompanies atherosclerosis and bronchial asthma is influenced by heparin and heparan sulfate (Burden and Buhler, 1988). Both exhibit antiproliferative effects for smooth muscle of the vasculature (including pulmonary), airways, intestine, and contractile cells such as fibroblasts and renal glomerular mesangial cells. Antiproliferative effects can be correlated with molecular size and sulfation of heparin. Endogenous heparin has been implicated in diseases characterized by smooth muscle proliferation. Manipulation of selected members of the heparins may offer a therapeutic alternative to treatment of this disease (Tyrrell et al., 1995). Heparin liberates lipoprotein lipase and can decrease serum triglyceride concentrations (Adams, 1995b).

Drug Disposition. The complex chemistry of heparin leads to complex disposition. Absorption and distribution of heparin are limited by its large size and polarity. Studies characterizing its elimination are generally based on response to therapy (i.e., changes in the activated partial thromboplastin time [APTT]. However, more recent studies in animals have been based on detection of the drug in blood (Kellerman et al., 1996). Absorption of heparin after oral administration or by aerosolization is negligible; as such, heparin is a "parenteral" anticoagulant. Heparin is metabolized by heparinase in the liver and by reticuloendothelial cells. Metabolites of heparinase activity are excreted in the urine. The elimination half-life appears to be molecular weight dependent, with LMW compounds having a half-life two to three times that of endogenous heparin. The half-life is prolonged in renal or liver failure (Freedman, 1992).

Preparations. Because heparin is a heterogeneous mixture, only about 33% of the molecules in the drug preparation inhibit coagulation, and correlation between heparin plasma concentration and anticoagulant activity is not possible. Correlation between dose and response is further complicated by differences in effects based on molecular weight. The concentration of heparin is standardized by bioassay as units of activity. Heparin is available as a sodium or lithium salt. The sodium salt is usually the preferred preparation for in vivo use.

Side Effects and Toxicities. Heparin stands out as a drug that will interact with many other drugs. Heparin should not be mixed with any other drug. Hemorrhage is the major complication of heparin therapy, occurring in 18% to 22% of human patients receiving heparin (Freedman, 1992). Hemorrhage is less likely to occur with low dosages and constant intravenous infusion (as opposed to intermittent intravenous administration). Hypersensitivity may play a role in hematoma formation (Grodman-Gross and Sastri, 1987). The incidence of hemorrhage can be reduced by (1) confirmation of the need for therapy; (2) use of the appropriate dose and frequency; (3) avoidance of combination therapy with other antihemostatic drugs, including aspirin and other salicylates; and (4) monitoring of the effects of therapy with clotting or coagulation tests.

At high doses, heparin is also antithrombotic. At higher doses, the APTT can be useful for assessing the likelihood of hemorrhage. Monitoring APTT is less useful when low doses of heparin are given. Heparin is contraindicated for the bleeding patient and for disseminated intravascular coagulopathy (DIC) unless replacement blood or plasma therapy is given (see later discussion of clinical indications). Excessive therapy (theoretically) might be treated with protamine sulfate, a compound that complexes with heparin. It is dosed according to the amount of heparin to be neutralized (see discussion of protamine earlier).

Thrombocytopenia has been reported in 5% to 30% of human patients receiving heparin and is more likely to occur with bovine as opposed to porcine preparations (Freedman, 1992; Greinacher et al., 1992; Shumate, 1995). Two types (type I and type II, similar to type A and type B adverse reactions) of thrombocytopenia have been described. Several days of therapy are necessary for type I thrombocytopenia to occur; it resolves once therapy is discontinued. Type I thrombocytopenia may occur less frequently with LMW heparins. Type II thrombocytopenia occurs in fewer people, is more severe, is rapidly fulminating, and is characterized by a longer time to onset (6 to 10 days). Type II thrombocytopenia may be an allergic response to the secondary and tertiary structures of heparin and has caused paradoxic thrombosis (Freedman, 1992). As with type I thrombocytopenia, the incidence of type II thrombocytopenia is likely to be less with LMW heparins.

A small number of human patients have developed skin necrosis with both unfractionated and LMW heparins. Lesions are similar to those caused by toxic epidermal necrolysis and can be lethal. The cause is unknown.

In human patients receiving long-term therapy, heparin has induced osteoporosis. The mechanism is not known but does not seem to involve prostaglandin E_2. The effect is more dramatic with unfractionated heparins. Low-molecular-weight heparins have an "osteopenic" or calcium-sparing effect, although the sequelae and nature of this effect are not characterized (Freedman, 1992).

Heparin (both LMW and fractionated products) causes increased serum alanine transaminase and aspartate transaminase levels in up to 93% of human patients receiving heparin. The increases peak approximately 7 days into therapy and then return to normal, with no obvious detrimental clinical sequelae. Heparin also interferes with and falsely increases bile acids. When used as an in vitro anticoagulant, heparin falsely increases blood urea nitrogen, bile acids, and sodium and potassium salts. Finally, heparin can interfere with several hormones. It interferes with thyroid hormones, causing decreases in both thyronine and thyroxine. It is a predictable and potent inhibitor of aldosterone secretion in human patients, causing natriuresis and the potential for hyperkalemia, particularly in predisposed patients (Aull et al., 1990; Oster et al., 1995). The effects of heparin on the renin-angiotensin-aldosterone system may be responsible for its antihypertensive effects (Susic et al., 1993).

Clinical Indications and Use. Clinical indications for heparin therapy include the prevention or treatment of venous or pulmonary embolism (e.g., nephrotic syndrome, autoimmune hemolytic anemia, hyperadrenocorticism, or heartworm disease) and atrial fibrillation with embolization (e.g., feline cardiomyopathy) and as an anticoagulant for diagnostic use and blood transfusion. Heparin is used in conjunction with blood and plasma for the treatment of DIC. Heparin remains the drug of choice when rapid anticoagulant activity is necessary in acute thrombosis. Heparin not only prevents further thrombosis but also facilitates resolution of the thrombus, promoting recanalization through activation of tissue plasminogen activator (Freedman, 1992) and stimulating angiogenesis. Efficacy of therapy does not seem to be related to the anatomic location of the thrombus.

Low-molecular-weight heparins (e.g., enoxaparin) have been studied in humans. Advantages when compared with HMW heparins include specificity of action; better absorption after subcutaneous injection, and prolonged elimination half-life. Reduced incidence of bleeding has also been suggested as an advantage of LMW heparins, although this is controversial (Frydman et al., 1988; Freedman, 1992).

For thrombosis, heparin is administered parenterally; deep subcutaneous or intrafat injection prolongs persistence of therapeutic concentrations. Large hematomas can occur with deep intramuscular injection. Heparin is also administered intravenously, either intermittently or as a constant infusion. In human patients, the use of weight-based nomograms to determine initial and maintenance heparin infusion rates results in a higher percentage of patients reaching the targeted activated thromboplastin time (ATT) range earlier in the course of therapy (Gunnarsson et al., 1995) Monitoring is particularly important to establish effective doses. Doses range from 150 to 250 U/kg in dogs and from 250 to 375 U/kg in cats every 8 hours. The dose of heparin in normal cats necessary to maintain therapeutic concentrations of heparin (as established in people, 0.35 to 0.7 U/mL) in one study was 300 U/kg of heparin every 8 hours (Kellerman et al., 1996). Monitoring APTT is less useful when low doses of heparin are given. In human patients (and possibly dogs), the dose of heparin necessary to control coagulation may be greater than that in the normal patient who is not suffering from a coagulopathy (Mungall et al., 1989).

For most causes of thromboembolism, therapy is more likely to be successful in patients if heparin is administered at a rate to cause the ATT time to be 1.5 to 2.5 times baseline or the activated clotting time (ACT) to be 1.2 to 1.4 times baseline (Gunnarsson et al., 1995; Hawkins, 1995). A baseline should be established before therapy is begun, and monitoring should occur 2 hours after a subcutaneous dose. Replacement of ATIII should accompany heparin therapy when indicated (e.g., nephrotic syndrome, DIC). Gradual discontinuation of heparin therapy has been recommended to avoid a "hypercoagulable" state (Hawkins, 1995). Long-term heparin therapy can be accomplished at home with subcutaneous injections, or warfarin therapy can be implemented (see later discussion of vitamin K antagonists).

For prevention of pulmonary thromboembolism, heparin can be administered at a lower dose (30 to 75 U/kg). Monitoring ACT or ATT may not be useful at these doses. Hemorrhage, however, remains a potential side effect in at-risk patients (i.e., those undergoing surgery).

In patients suffering from severe heartworm disease, low-dose heparin given 1 to 2 weeks before treatment and 3 to 6 weeks after treatment improves survival rates compared with no treatment and with aspirin therapy (Rawlings and Calvert, 1995). In the event of thrombosis associated with adulticide therapy, heparin should be administered (50 to 70 U/kg every 8 hours) for at least 7 days (assuming the platelet count increases to above 150,000/mm^3).

The use of heparin for treatment of DIC remains controversial (Greene and Thomas, 1995). Its efficacy for DIC depends on adequate concentrations of ATIII (≥40% of normal). Replacement therapy with either whole fresh blood or fresh or fresh frozen plasma is indicated if ATIII levels are not normal or for actively bledding patients. A loading dose is generally followed by a maintenance dose; the loading dose can be preincubated with blood or plasma in order to maximize effects on ATIII. Maintenance dosing should be based on changes in APTT rather than on a fixed dose. This is particularly true in patients suffering from DIC because the synthesis of cofactors varies among patients with DIC. Although normal dogs respond rapidly to heparin therapy, identification of changes in APTT in DIC patients may be difficult. Neutralization of heparin with polybrene (hexadimethrine bromide) (Greene and Thomas, 1995) can be used to distinguish changes in the APTT due to heparin from those due to DIC once a baseline APTT has been established. The APTT should be prolonged by 1.5-fold to 2-fold. The dose of heparin should vary with the severity of DIC, ranging from 5 to 10 U/kg to 750 to 1000 U/kg (severe with organ damage due to microthrombosis) every 8 hours. Heparin should not be abruptly discontinued in patients with DIC because of the risk of rebound hypercoagulability associated with ATIII deficiency.

Nonanticoagulant uses of heparin are increasing in human medicine. Anecdotal reports in humans indicate that heparin can be beneficial for the treatment of asthma and allergic inflammation.

Vitamin K Antagonists (Oral Anticoagulants)

The oral anticoagulants differ primarily in their duration and magnitude of effect. Studies of their importance in veterinary medicine have focused primarily on their toxic rather than their therapeutic indications (Schulman et al., 1986), although these drugs are being used increasingly to treat thromboembolic diseases.

Chemistry. The vitamin K antagonists consist of two groups: the coumarin derivatives (dicoumarol and warfarin) and the indandione anticoagulants. Both interfere with the hepatic synthesis of vitamin K–dependent clotting factors II, VII, IX, and X and anticoagulant proteins C and S (see Fig. 7–9) (Aull et al., 1990). They block the reduction of vitamin K by vitamin K epoxide after its use in factor synthesis, thus effectively reducing the concentration of vitamin K. Two points are important based on this mechanism. First, the anticoagulant activity occurs only in vivo, and, second, there is a delay in anticoagulant activity (and therefore therapeutic or toxic effect) for 8 to 12 hours because of the persistence of factors synthesized before administration. Factor VII has the shortest half-life and therefore is the first factor to become deficient. Antithrombotic effects occur in 4 to 6 days after therapy is begun, however, as serum concentrations of factors IX and X decrease. Serum concentrations of the anticoagulant protein C also decrease, but more rapidly than clotting factors, thus possibly rendering the patient "hypercoagulable." Heparin therapy might be used for the first 2 to 5 days after warfarin therapy is begun to avoid this hypercoagulable state.

Disposition. The vitamin K antagonists are rapidly and completely orally absorbed. Warfarin is 75,000 times more soluble in water than is dicoumarol and is characterized by much better oral bioavailability (Adams, 1995b). Peak levels occur in 1 hour. There are, however, marked differences in product bioavailability, and products should be interchanged with caution. For products used as rodenticides, warfarin derivatives often have a drug half-life up to 7 days, whereas the indandione diphacinone has an elimination half-life of 30 days (Schulman et al., 1986). All coumarin derivatives are highly bound to serum albumin, limiting the distribution volume to plasma volume. Vitamin K antagonists are metabolized by the liver to inactive metabolites by the cytochrome P450 system and subsequently conjugated to glucuronide. They undergo an enterohepatic cycle. Warfarin has not been studied in dogs and cats.

Preparations. Vitamin K antagonists are prepared for therapeutic use as tablets and solutions (e.g., warfarin, dicoumarol). They are, however, more commonly used as oral rodenticides.

Drug Interactions. A variety of factors can increase the activity of warfarin anticoagulants. Hypoproteinemia, antimicrobial therapy, hepatic disease, hypermetabolic states, pregnancy, and the nephrotic syndromes are some examples. Drug interactions are most significant when used therapeutically for chronic treatment. Because they are highly protein bound, they will be displaced by (or will displace) other drugs that are protein bound, and their anticoagulant effects may be increased to the point of toxicity. Examples include acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs. Drug interactions occur with other antihemostatic agents.

Clinical Use. Clinical use of the coumarin derivatives in dogs and cats is increasing as monitoring techniques improve and doses are refined. The high incidence of recurrent thromboembolism in cats receiving aspirin has led to renewed interest in the use of warfarin for management of arterial thromboembolism. Currently, cardiologists are recommending use of warfarin even in the absence of prior thromboembolic events once adequate left atrial enlargement (left atrial to aortic ratio < 2) has been confirmed by echocardiography (Harpster and Baty, 1995). The drug is discontinued if atrial size should normalize (ratio of > 1.25).

Warfarin therapy for humans is characterized by doses that vary as much as 20-fold. Variability should be anticipated as a result of species differences in drug disposition, warfarin preparations, the target disease, and the presence of other drugs that may potentially interact with warfarin. Accurate dosing should be based on drug-response monitoring. For long-term anticoagulant needs, or in combination with heparin (100 U/kg every 8 hours) for acute treatment of thromboembolism, warfarin can be administered at 0.1 to 0.2 mg/kg (or one fourth to one half of a 1.0-mg tablet in cats) orally every 24 hours (Harpster and Baty, 1995; Sisson and Thomas, 1995).

The prothrombin time (PT) should be measured at baseline. Heparin therapy (when also being used) may prolong the prothrombin (as well as ACT and ATT), but a baseline should still be established. Warfarin therapy should be monitored by 4 to 5 days of therapy. Beginning monitoring earlier may help detect changes more easily. Monitoring techniques should be standardized. An optimum sampling time of 2 hours has been recommended (Harpster and Baty, 1995). The target response to warfarin therapy varies. Recommendations have included an increase in baseline prothrombin of 1.3 to 1.6 times baseline to 1.5 to 2.5 times baseline (Harpster and Baty, 1995).

A standardized approach has been recommended based on an international reference preparation of standardized human brain thromboplastin. An International Normalization Ration (INR) is determined for the patient (INR = patient prothrombin/control PT^{ISI}), where ISI is the International Sensitivity Index of the thromboplastin control used to determine the prothrombin. The ISI is provided by the manufacturer of the thromboplastin control. Standardization is important because controls can vary by more than twofold. A target INR of 2.0 to 3.0 has been recommended for prevention of feline thromboembolism while minimizing the risk of bleeding. Either the dose or the interval can be manipulated to achieve the target INR (or prothrombin). Tablet size restrictions may, however, make it difficult to fine-tune warfarin therapy. The dosing interval might be prolonged to as long as 48 hours for some patients (Hawkins, 1995). Heparin therapy can be discontinued approximately 3 days after warfarin therapy is begun; prothrombin should be expected to decrease as a result. After the patient is sent home, monitoring can be decreased to 2-week intervals.

Warfarin therapy has been combined with aspirin to treat or prevent recurrent thromboembolism or increased risk of thromboembolism. Although the combination is rational, the risk of bleeding is intensified. Not only are both platelets and coagulation factors targeted with this combination, but drug interactions between these two highly protein-bound drugs can also complicate safe therapy.

Toxicity. Toxicity manifested as hemorrhage has been the major veterinary medical concern with vitamin K antagonists. Secondary poisoning resulting from the ingestion of a rodent that has eaten treated bait is the most common cause of toxicity. Toxicity can also occur, however, by overdosing warfarin for treatment of thromboembolism. Treatment for anticoagulant rodenticide toxicity is symptomatic and specific. Specific therapy is vitamin K. Vitamin K_1 is a very effective antidote, but it must be given as long as the anticoagulant is present in the body at toxic levels. This time varies, depending on the drug, from several days to several weeks after ingestion. Vitamin K_3 (menadione) is much less expensive but is also far less effective and never should be used as the sole antidote in cases of severe coagulopathy. Treatment with vitamin K will preclude the therapeutic benefits of warfarin for up to 3 weeks.

Fibrinolytics (Thrombolytics)

Fibrinolytic agents increase the activity of plasmin (fibrinolysin), the endogenous compound that is responsible for dissolving clots (Witty et al., 1994).

Streptokinase and Streptodornase

Streptokinase and streptodornase are synthesized by streptococcal organisms. Urokinase is prepared from cultures of human renal cells. Streptokinase, streptodornase, and urokinase are used in the treatment of wounds that do not respond to antibacterial therapy, burns, ulcers, chronic eczemas, ear hematomas, otitis externa, osteomyelitis, chronic sinusitis, or other chronic lesions. They are available as powders for local or systemic administration. Streptokinase may be useful for the treatment of feline thromboembolic disease. In an experimental model, streptokinase reduced mean thrombus weight after administration of a loading dose (90,000 IU/cat) and a constant maintenance infusion of 45,000 IU (studied only for 3 hours). Clinical use of streptokinase has not been reported (Sisson and Thomas, 1995).

Tissue Plasminogen Activator

Tissue-type plasminogen activator (tPA) activates plasminogen bound to fibrin. Its use should be limited to cases of thrombosis (rather than prevention). Some studies have indicated a potential use for tPA for dissolution of thrombi in cats, but side effects need to be minimized before general use of the drug can be accepted. Although 50% percent of cats with spontaneous aortic thrombosis treated with tPA

(0.25 to 1.0 mg/kg per hour for a total dose of 1 to 10 mg/kg) had resolution of clinical signs, 70% of the cats treated died from reperfusion injury, heart failure, or other side effects (Sisson and Thomas, 1995).

Clinical Use

Cost and lack of refined doses and selectivity have limited the use of thrombolytic drugs for treatment of (pulmonary) thromboembolism in dogs and cats.

Antithrombotics

Platelet activity is controlled by substances generated both outside and inside the platelet. Adenophosphate, prostaglandins, and thromboxane, serotonin, and cAMP and GMP are generated within the platelet where they interact with platelet receptors or with the platelet itself. Modulation of all platelet activity can be achieved by interaction with these compounds. Drugs used to modify platelet activity in veterinary medicine include aspirin and related compounds. Ticlopidine has been used empirically (results not validated) but not studied. Propranolol has been found to be ineffective as an inhibitor of platelet activity (Allen et al., 1985; Greene and Thomas, 1995).

Ticlopidine is an antiplatelet drug studied extensively in human patients with thromboembolic diseases. The drug appears to affect platelet membranes and limits platelet aggregation in response to a number of stimuli (Adams, 1995). Inhibition occurs in 2 to 5 days and is irreversible. A dose of 62 mg/kg every 24 hours inhibits platelet aggregation in normal animals, but higher doses may be necessary in the presence of thromboembolic disease (Adams, 1995; Boudreaux et al., 1991a). Dipyridamole is a vasodilator that inhibits cAMP phosphodiesterase and increases cAMP in the platelet. When used alone, it minimally affects platelet activity, but acts synergistically with aspirin to inhibit platelet activity (Boudreaux et al., 1991b).

Aspirin causes an irreversible and thus long-lasting negative effect on platelet activity, which is clinically manifested as prolonged bleeding time. Aspirin irreversibly inactivates prostaglandin G and H synthetase, the enzyme that catalyzes the initial conversion of arachidonic acid to thromboxane A_2. Two types of this enzyme are present: the constitutive form responsible for conversion of arachidonic acid to prostaglandin H (and ultimately thromboxane) and an inducible form that activates cells in response to growth factors during inflammation. The antiplatelet effects of aspirin result from acetylation of the constitutive form of the enzyme (Patrono, 1994). Platelets are not able to synthesize proteins and thus cannot regenerate the enzyme necessary for thromboxane formation. The irreversible nature of platelet inhibition allows aspirin administration to occur at 3-day or longer intervals. Reduced formation of the various eicosanoids responsible for platelet aggregation and coagulation accounts for the variety of different pharmacologic (therapeutic and toxic) responses to aspirin. Side effects of aspirin can, however, be minimized by taking advantage of the dose-response relationship between aspirin and its many pharmacologic effects.

The antiplatelet effect of aspirin can be separated to a large degree from its other actions by administration of a low dose (0.5 mg/kg every 12 hours in normal dogs; 10 mg/kg in heartworm-infested dogs; 25 mg/kg twice weekly in cats) (Jackson, 1987; Patrono, 1994; Adams, 1995b). Although experimental studies reveal antiplatelet activity, clinical response is variable (Rawlings et al., 1983a, b). Aspirin, however, remains a component of therapy directed toward prevention and treatment of arterial thrombosis (Chastain, 1987; Patrono, 1994; Hillman, 1996), including severe pulmonary arterial thrombosis associated with heartworm disease (Rawlings and Calvert, 1995). Coupled with cage confinement, aspirin (4 to 6 mg/kg per day) administered for 2 to 3 weeks before caparsolate therapy may improve survival after treatment (Rawlings and Calvert, 1995). Aspirin is still the most commonly used drug for prevention of arterial thrombosis in cats (25 mg/kg orally every 72 hours) despite the lack of clinical proof of efficacy (Sisson and Thomas, 1995). Recurrence of thrombosis may, however, be as high as 75%.

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Principles of Antimicrobial Therapy

8

Dawn Merton Boothe

INTRODUCTION

IDENTIFYING THE TARGET ORGANISM
- Empirical Antimicrobial Therapy
- Culture and Susceptibility Testing
- Interpreting Culture and Susceptibility Tests
  - Breakpoint MIC
  - Evaluation of the Relative Efficacy of Antimicrobials
  - Relationship between MIC, PDC, Tissue Concentration, and Drug Efficacy

IDENTIFYING HOST FACTORS
- Detrimental Effects of Local Environment on Drug Activity
- Host Factors that Facilitate Drug Efficacy

IDENTIFYING DRUG FACTORS
- Mechanisms of Drug Action
- Drug Disposition
  - Absorption
  - Distribution
  - Drug Elimination
- Resistance to Antimicrobials
  - Mechanisms of Transmission
  - Biochemical Mechanisms of Resistance
- Avoiding Antimicrobial Resistance
- Drug Toxicity

ENHANCING ANTIMICROBIAL EFFICACY
- Proper Dose and Route
- Combination Antimicrobial Therapy
  - Synergism and Antagonism
  - Polymicrobial Infections

MISCELLANEOUS CONSIDERATIONS
- Convenience and Cost
- Evaluating Response to Therapy

INTRODUCTION

The goal of antimicrobial therapy is to achieve effective concentrations of an appropriate drug at the site of infection while avoiding toxic concentrations of drug in plasma or organs. Every decision concerning antimicrobial therapy for the infected patient can be challenging (Table 8–1). Each decision must take into account microbial, drug, and patient factors (i.e., the chemotherapeutic triangle) (Fig. 8–1 and Table 8–2). Ideally, antimicrobial selection is based on spectrum of microbial activity, patient pharmacokinetics, and drug pharmacodynamics. The terms *antibiotic, antibacterial*, and *antimicrobial* are often used interchangeably, although they actually have different meanings. *Antibiotics* are chemicals produced by organisms intended to suppress other organisms (generally bacterial, but not exclusively so). The term *antimicrobial* refers to any compound, whether natural, synthetic, or semisynthetic, that will suppress growth of microbes. *Microbes* generally refers to bacterial organisms but also includes fungal and other organisms.

The first question to be addressed in the selection of an antimicrobial is the need for therapy. It is beyond the scope and intent of this chapter to determine whether or not antimicrobial therapy is indicated. Fever, inflammation, dysfunction of organs as based on clinical signs or clinical pathology, and structural changes as indicated by radiography or other imaging techniques support but do not conclusively prove infection. Cytology, especially with Gram

Table 8–1. Decisions To Be Made During Antimicrobial Therapy

1. Determine the need for antimicrobial therapy
2. Determine the source of infection and target organism
   - Empirical therapy
   - Culture and susceptibility testing
3. Assess clinical status
   - Immune status
   - Physiologic status
   - Organs susceptible to toxicity
4. Determine host factors detrimental to drug efficacy
   - Difficult to penetrate organs
   - Magnitude of inflammation at the site
5. Select the antimicrobial
   - Single versus combination therapy
   - Drug pharmacokinetics
6. Determine dosing regimen
7. Assess response
   - Efficacy
   - Toxicity
8. Reevaluate antimicrobial protocol
9. Discontinue therapy

Table 8–2. Criteria for Antimicrobial Selection (General)

- Microbial factors
  - Target organism
  - Susceptibility pattern
  - Bactericidal versus static needs
- Host factors
  - Effects of disease on drug disposition
  - Effects of disease on drug toxicity
  - Severity of illness
  - Target site
    - Accessibility
    - Environmental effects
  - Immunocompetence
- Drug factors
  - Mechanism of action
    - Toxicity
    - Resistance
  - Disposition characteristics
    - Distribution
    - Route of elimination
    - Convenience
  - Toxicity
  - Availability
  - Cost

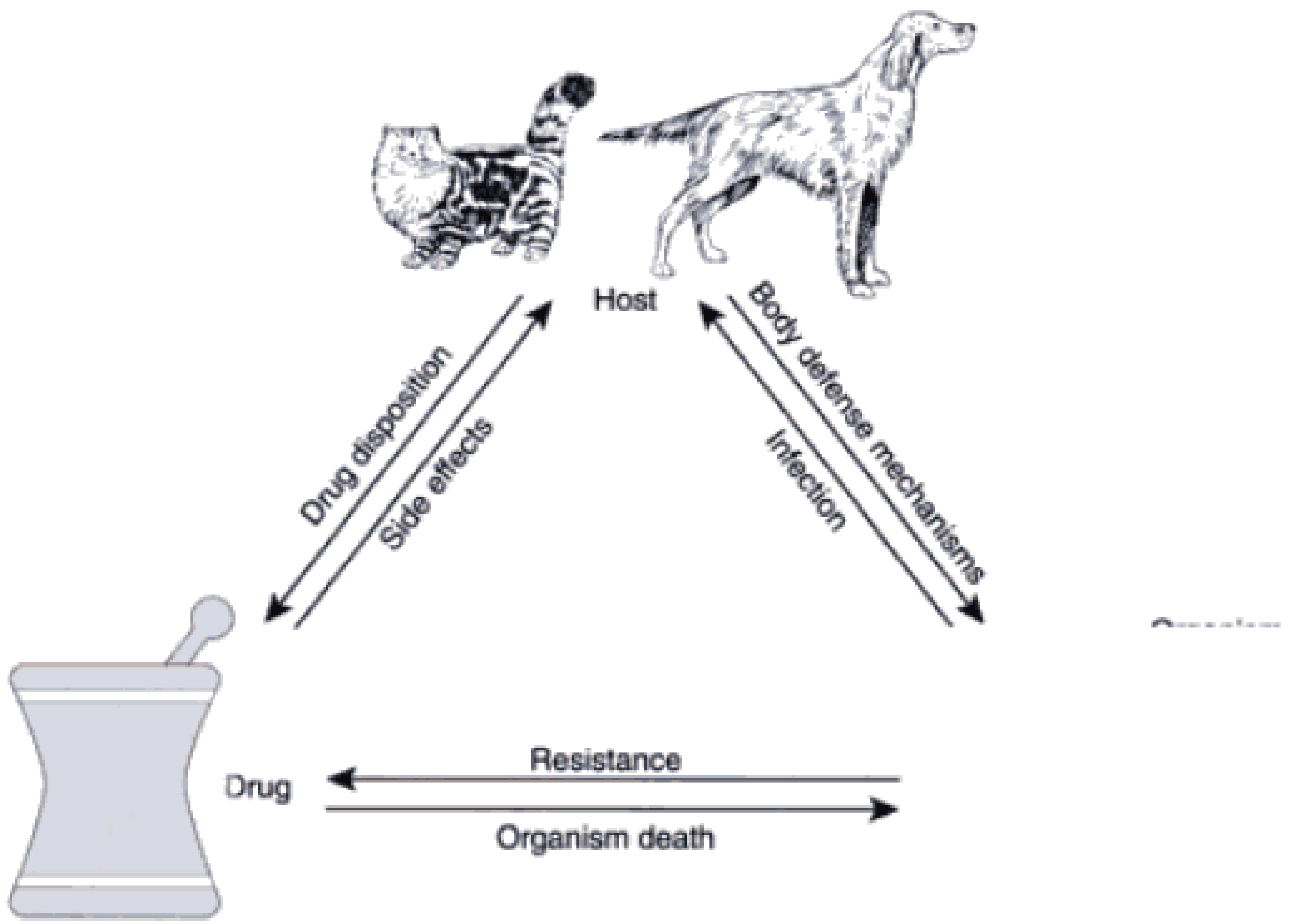

Figure 8–1. In contrast to other drug therapies, antimicrobial therapy involves not only the host and drug but also the microbe. Interactions among the three complicate successful antimicrobial therapy.

staining, and cultures can be used to document the presence of organisms, but evidence of infection still must be made based on other supportive data. The definitive support for antimicrobial therapy is clinician discretion. Cytology that reveals organisms phagocytized by neutrophils or mononuclear cells is supportive of infection. Predominance of mononuclear cells may indicate chronicity of the infection, suggesting more aggressive therapy. This chapter emphasizes the rational basis for decision making in the selection of the proper antimicrobial. Indiscriminant use of antimicrobials is discouraged for many reasons, among them being the risk of superinfection, development of resistant organisms, cost, inconvenience, and increased host toxicity.

IDENTIFYING THE TARGET ORGANISM

Empirical Antimicrobial Therapy

Once the need for antimicrobial therapy has been identified, the first decision to be made is to identify the target organism. Therapy can be empirical based on historical data (Table 8–3) or based on organisms identified by culture at the site of infection (Fig. 8–2) (Yoshikawa, 1984). Careful clinical evaluation of the patient may reveal the source of infection. Although oral, respiratory, skin, and urinary tract infections may be identified easily, bacteremia

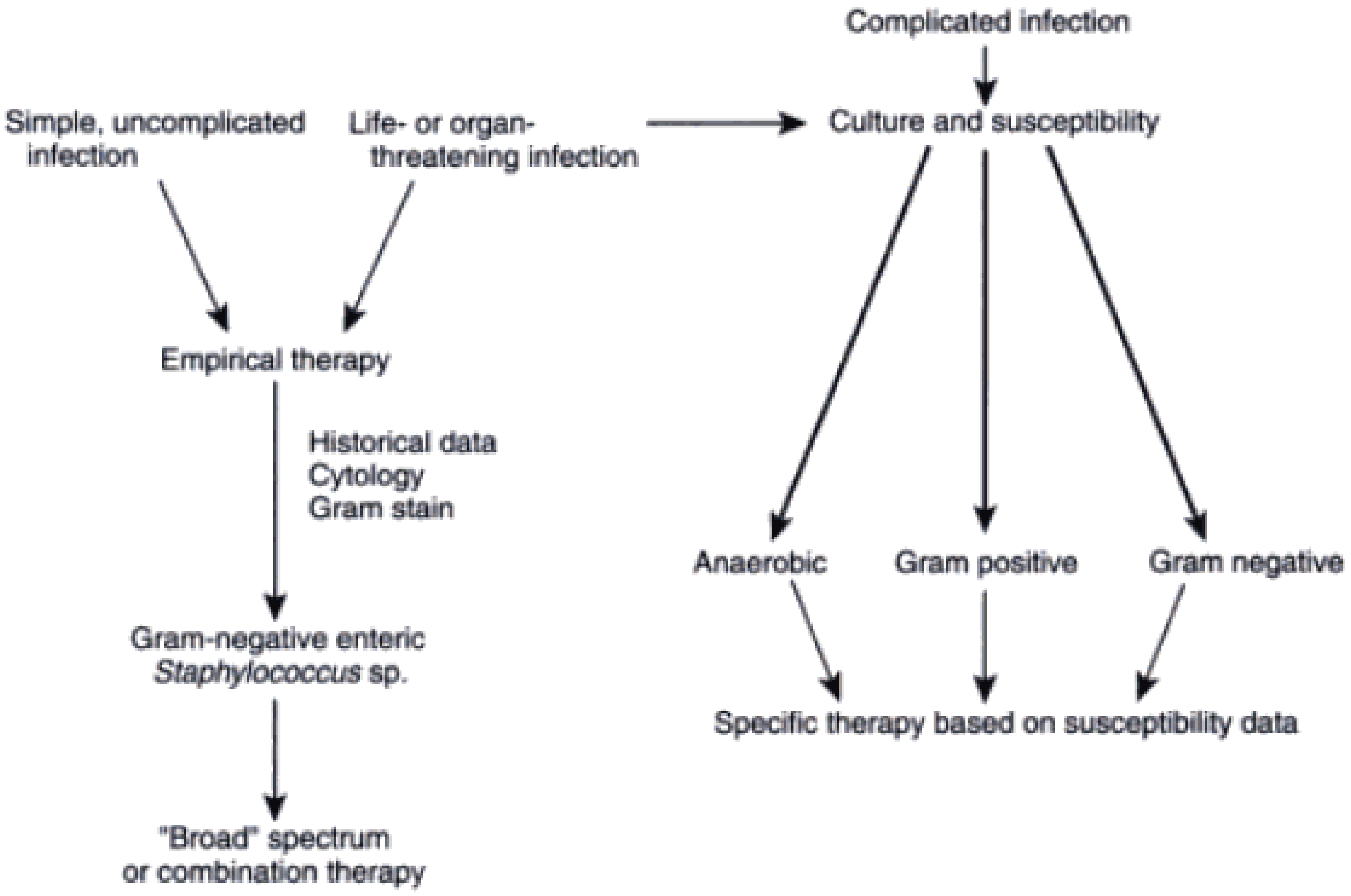
Complicated infection
Simple, uncomplicated infection
Life- or organ-threatening infection
Culture and susceptibility
Empirical therapy
Historical data
Cytology
Gram stain
Gram-negative enteric
Staphylococcus sp.
"Broad" spectrum or combination therapy
Anaerobic
Gram positive
Gram negative
Specific therapy based on susceptibility data

Figure 8–2. Successful antimicrobial therapy begins with identification of the target organism. Identification can be based on empirical therapy, gram-positive (*Staphylococcus* sp.) and gram-negative coliforms being common pathogens, or with culture and susceptibility data. Organisms are classified as gram positive (aerobic), gram negative, and anaerobic. This distinction is important in the decision regarding the spectrum of drugs to use.

Table 8–3. Normal Flora and Clinically Significant Infections by Organ System (Dogs and Cats)

Organ	Organism	Comment
Blood	*Staphylococcus intermedius* (D: 25%–35%)*, †, ‡	
	Streptococcus spp. (D: 18%–21%)†	
	Enterobacter cloacae (D: 3%–8%, C: 7%)†	
	Escherichia coli (D: 35%–45%*; D: 18%–71% & C: 14%)†	
	Klebsiella pneumoniae (D: 25%–35%*; C: 14%)†	
	Proteus (D: 14%)†	
	Pseudomonas aeruginosa (D: 10%–20%)	
	Salmonella (D: 11%–13%; C: 29%)†	
	Obligate anaerobes (D: 10%–20%)	
Endocarditis†	*Staphylococcus intermedius* (D: 6%–33%)	
	Streptococcus (D: 12%–26%)	
	Escherichia coli (D: 6%–30%)	
	Erysipelothrix rhusiopathiae (D: 19%)	
	Corynebacterium spp. (D: 19%)	
Respiratory		
Upper	*Staphylococcus intermedius* (D: 30%–35%)§, ‖, ¶	Have been isolated from nasal swabs,** tonsillar and pharyngeal swabs,‖ or tracheal and lung swabs¶
	Streptococcus (15%–27%)§, ‖, ¶	
	Corynebacterium spp.§, ‖, ¶	
	Escherichia coli§ (15%–29%)§, ‖	
	Klebsiella pneumoniae (D: 10%–15%)‖, ¶	
	Moraxella§, ¶	
	Neisseria§, ‖	
	Pasteurella multocida (D: 15%–34%; C: >50%)§, ‖	
	Proteus (C: <10%)§, ‖	
	Pseudomonas§ (6%–34%)§, ‖	
	Bacteroides‖	
	Clostridium spp.§	
	Fusobacterium‖	
Rhinitis, sinusitis	*Escherichia coli*	
	Pasteurella multocida	
	Proteus	
	Pseudomonas sp.	
Tracheobronchitis	*Bordetella*	
Lower	*Staphylococcus intermedius* (D: 10%–15%)	Normal bronchi and lungs are sterile distal to first bronchial division
	Escherichia coli (D: 30%–40%; C: 15%–20%)	
	Bordetella (D: 10%–15%)	
	Enterococcus	
	Klebsiella pneumoniae (D: 15%–20%; C: <10%)	
	Pasteurella multocida (C: >50%)	
	Pseudomonas	
	Proteus mirabilis (D: <10%)	
Pleuritis	*Actinomyces, Bacteroides, Corynebacterium, Fusobacterium, Nocardia, Pasteurella, Staphylococcus, Streptococcus*	
Gastrointestinal		
Oral cavity	β-Hemolytic *Streptococcus*	Isolates from healthy dogs§
	Staphylococcus epidermidis§	
	Acinetobacter§	
	Escherichia coli§	
	Moraxella§	
	Neisseria§	
	Pasteurella§	
	Proteus§	
	Pseudomonas§	
	Obligate anaerobes (80%–90%)	
Small intestine	*Escherichia coli, Klebsiella*§, ¶	Enteropathogenic bacteria in the stomach or small intestine associated with enterotoxin¶ or mucosal invasion
Enterobacteriaceae§	*Campylobacter fetus*¶	
	Moraxella	
	Neisseria	
	Proteus sp.	
	Pseudomonas sp.	
	Salmonella typhimurium§, ¶	
	Shigella§	
	Vibrio cholerae¶	
	Vibrio parahaemolyticus§	
	Yersinia enterocolitica¶	
	Clostridium perfringens (type A)¶	
	Bacillus§, ¶	
Large intestine	Enterobacteriaceae	Normal microflora; anaerobic make up 90% of microflora
Enterobacteriaceae§	Anaerobes	
Peritonitis		
Hepatobiliary	Enterobacteriaceae	
	Escherichia coli	
	Enterobacter	
	Klebsiella	

Table continued on following page

Table 8–3. Normal Flora and Clinically Significant Infections by Organ System (Dogs and Cats) *Continued*

Organ	Organism	Comment
Genital	*Staphylococcus intermedius* (D: 15%–25%)§	Normal microflora of distal urethra and prepuce§
	Acinetobacter§	
	Escherichia coli (30%–35%)§	
	Klebsiella§	
	Moraxella,§ *Haemophilus*§	
	Pasteurella multocida (10%–25%)§	
	Proteus sp.§	
	Pseudomonas aeruginosa (<10%)	
	Obligate anaerobes (C: 10%–25%)	
	Mycoplasma sp.§	
	Ureaplasma sp.§	
	Staphylococcus intermedius (D: 15%–25%)§	Normal microflora of canine vagina§
	Staphylococcus epidermidis§	
	Streptococcus canis, S. faecalis, S. viridans, S. zooepidemicus§	
	Corynebacterium§	
	Acinetobacter§	
	Citrobacter§	
	Enterobacter§	
	Enterococcus§	
	Escherichia coli (30%–35%)§	
	Haemophilus§	
	Klebsiella§	
	Micrococcus§	
	Moraxella,§ *Neisseria*§	
	Pasteurella multocida (15%–25%)	
	Proteus§	
	Pseudomonas aeruginosa (<10%)§	
	Obligate anaerobes (C: 10%–25%)	
	Mycoplasma§	
	Ureaplasma§	
Urinary Tract	*Staphylococcus intermedius* (D: <10%)	
	Enterococcus faecalis (D: <10%)	
	Escherichia coli (40%–50%)	
	Klebsiella pneumoniae (10%–15%)	
	Pasteurella multocida (C: 10%–15%)	
	Proteus mirabilis (10%–15%)	
	Pseudomonas aeruginosa (C: <10%)	
Central Nervous System	*Brucella*	
	Pasteurella	
Ocular		
Conjunctiva	*Staphylococcus intermedius*,§, ¶ *S. albus*¶	Cultured from the conjunctival sac of clinically normal dogs or cats§, ¶
	β-Hemolytic *Streptococcus* (C: 15%–25%)§, ¶	
	Corynebacterium§, ¶	
	Escherichia coli¶	
	Moraxella§	
	Neisseria§	
	Pasteurella multocida (C: 10%–20%)	
	Pseudomonas§	
	Proteus	
	Bacillus§, ¶	
	Chlamydia psittaci (C: 50%–75%)	
	Mycoplasma¶	
Eye	*Leptospira*	
	Brucella canis	
	Clostridium tetani	
	Mycobacterium bovis	
Otitis Externa	*Staphylococcus intermedius* (D: 25%–30%)	
	Escherichia coli (D: 10%–20%)	
	Proteus mirabilis (D: 20%–25%)	
	Pseudomonas aeruginosa (D: 15%–25%)	
Skin	*Staphylococcus intermedius* (D: 60%–70%)	
	Escherichia coli (20%–30%)	
	Pasteurella multocida (C: >50%)	
	Proteus mirabilis (<10%)	
	Pseudomonas aeruginosa (D: <10%)	
Wounds, Abscesses	*Staphylococcus intermedius* (D: 25%–50%)	
	Escherichia coli (D: 20%–30%; C: 10%–20%)	
	Pasteurella multocida (C: 30%–40%)	
	Proteus mirabilis (D: 10%–20%; C: <10%)	
	Pseudomonas aeruginosa (D: 10%–20%)	
	Obligate anaerobes (25%–35%)	
Musculoskeletal		
Osteomyelitis	*Staphylococcus intermedius* (D: 40%–50%)	
	Staphylococcus aureus	
	Escherichia coli (D: 10%–20%)	
	Enterococcus faecalis (D: 10%–20%)	
	Proteus mirabilis (10%–20%)	

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*Numbers in parentheses refer to probable percentages of infections in this tissue that are caused by the organism, as cited by Aucoin (1993). Unless noted otherwise, the percentages refer to both dogs and cats (D = dog; C = cat). Note that the probable percentage is likely to vary geographically and may be biased toward patients referred to a specialty service.

†Numbers in parentheses refer to probable percentages of infection in this tissue that are caused by the organism, as cited by Greene (1990).

‡Number in parentheses reflects the range of percent cited by both Aucoin (1993) and Greene (1990).

§¶For each tissue, the symbol is defined in the Comment column.

**Organisms that are cultured from clinically healthy animals may be difficult to distinguish from those that cause infection.

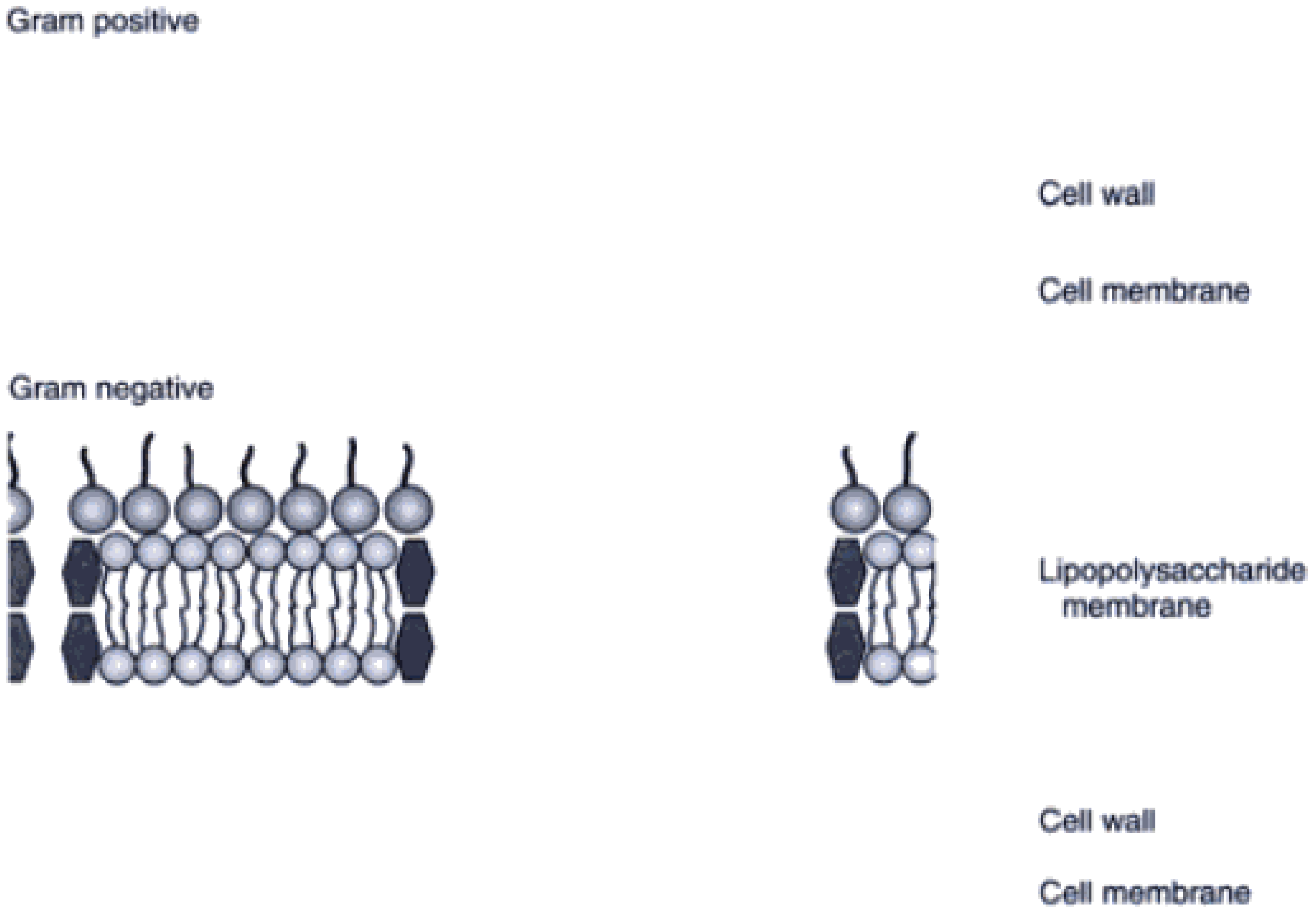


Figure 8–3. The gram-positive cell wall is thicker than the gram-negative cell wall, but the gram-negative cell wall is protected by an outer membrane.

and gastrointestinal infections are more insidious (Schimpff et al., 1989; Kapusnik et al., 1989).

The role of a properly collected specimen that has undergone Gram staining should not be overlooked when antimicrobial therapy is considered. A single organism indicates the need for antibiotic therapy; multiple organisms may represent contamination of the sample, floral colonization, or a polymicrobial infection (Kapusnik et al., 1989). Phagocytosis of an organism can be used to distinguish infection from simple colonization. The distinction between gram-negative and gram-positive organisms can be important. Gram stain characteristics differ according to the thickness of the cell wall (many layers thick in gram-positive compared with several layers thick in gram-negative organisms) and the presence of an external lipopolysaccharide (LPS) covering in gram-negative organisms that is not present in gram-positive organisms (Fig. 8–3). The external covering is also a barrier to drug movement into the bacterial organism (Fig. 8–4) (Neu, 1994). Finally, The LPS is the source of endotoxin responsible for the morbidity and mortality associated with many gram-negative infections. Both local and systemic effects can profoundly alter successful therapy. (see Chapter 11).

Identification of organisms without the benefit of a Gram stain or culture is problematic. The source of infection may help guide empirical antimicrobial therapy because some organisms are more likely to infect some body systems more than others. For example, genitourinary tracts are often infected with gram-negative aerobes, whereas abdominal infections generally are caused by gram-negative aerobes initially and then anaerobes (see Table 8–3) (Kapusnik et al., 1989; Greene, 1990). Granulocytopenic or otherwise immunoincompetent patients are more likely to be infected by aerobic gram-negative organisms. Pathogens often reflect the normal flora of infected sites: *Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumon-*

Figure 8–4. The outer cell membrane of gram-negative organisms is protected by a layer of lipopolysaccharides. Endotoxin, derived from the lipopolysaccharides, contributes to the mortality and morbidity of gram-negative infections. The membrane also presents a challenge to drug movement. Although lipid-soluble drugs can diffuse through the membrane, movement of water-soluble drugs must occur through channels in the membrane called *porins*. Reduction in porin size and thus drug movement is an important mechanism of resistance by gram-negative organisms against most antibiotics.

iae, and *Staphylococcus aureus* (see Table 8–3) or, particularly in critical patients, organisms from the alimentary canal or nosocomial organisms (Schimpff et al., 1989). Nosocomial organisms are characterized by complex resistant patterns that require more expensive and potentially toxic drugs for effective therapy. Without the benefit of specific organism identification, broad-spectrum or combination antimicrobials with a low incidence of resistance and toxicity should be selected for empirical therapy. A target organism should, however, be identified even if it is a presumed organism.

Culture and Susceptibility Testing

Blood, urine, respiratory secretions (collected by bronchoscopy) and other pertinent body fluids (i.e., pleural, peritoneal or cerebrospinal fluid [CSF]) should be carefully sampled before antimicrobial therapy is begun. Colonization by normal flora (see Table 8–3) can be difficult to distinguish from infection with normal flora using culture techniques. A pure growth is indicative of infection, particularly if greater than 10^5 colony-forming units are present per mL of sample. Colony counts are not feasible for most tissues (exceptions include urine). Cultures yielding successful growth only after incubation in enriched nutrient broth might be indicative of colonization only, not infection. Culture and susceptibility testing can prove beneficial if the infecting microorganism is resistant to the selected antimicrobial; the dose of the drug requires modification; or an equally effective, but less expensive drug is available (Washington, 1989). Repetitive cultures might be used to document antimicrobial secondary resistance that develops during therapy. Culture and susceptibility testing is particularly critical for patients that recently have been receiving antimicrobials. Even if antimicrobial therapy must begin immediately, culture and susceptibility data collected before the start of therapy may still be important to therapeutic success. For example, initial antimicrobial therapy is changed after receipt of culture and susceptibility data in up to 35% of critical care patients (Hardie, 1996).

Culture and susceptibility testing not only identifies the infecting organism(s) but also provides specific data regarding drug efficacy. The distinction between anaerobic and aerobic organisms is important because some drugs are effective against one group but not the other (e.g., fluorinated quinolones and aminoglycosides are not effective against anaerobic organisms; metronidazole is effective only against anaerobic organisms). In addition, infection by anaerobic organisms may indicate a microenvironment that negatively impacts drug efficacy (see later discussion).

Interpreting Culture and Susceptibility Tests

Two methods of bacterial culture, disk diffusion and tube dilution, are generally implemented. Each method provides different information. The disk diffusion method (e.g., Kirby Bauer) uses disks impregnated with a known amount of drug that diffuses into the agar at a known rate (Fig. 8–5) (Acar and Goldstein, 1996). The concentration of the drug in the agar correlates with the minimum inhibitory concentrations (MIC) of the drug. The agar is streaked with a standardized inoculum of the cultured organism. The concentration of the drug decreases with the distance (zone) diameter from the disk. Microbial growth that is inhibited by the drug will result in a zone of no growth (diameter, in millimeters) that surrounds the disk. Antimicrobial growth that is inhibited at a large diameter indicates a susceptible organism because it is likely that the drug concentration in the agar that inhibited growth is low enough that it can be achieved safely in the patient. Growth inhibited only as the disk is approached indicates that a higher concentration of drug must be achieved in the patient. If it is unlikely that this concentration can be reached in the patient at the recommended dose, an "R" is designated for the drug. The zone sizes at which an organism is considered resistant is established by the National Committee for Clinical Laboratory Standards according to stringent criteria and generally can be correlated with an MIC of the drug (see tube dilution method). The disk diffusion method thus might be considered a semiquantitative method in that drug concentrations achieved in the agar surrounding the disk can be roughly correlated with concentrations achieved in the patient serum. Not all organisms grow sufficiently rapidly for agar gel diffusion techniques. Generally, only rapidly growing aerobic organisms can be tested using these methods.

In contrast to the disk diffusion method, the tube dilution method provides quantitative data regarding the amount of drug necessary to inhibit microbial growth (Fig.

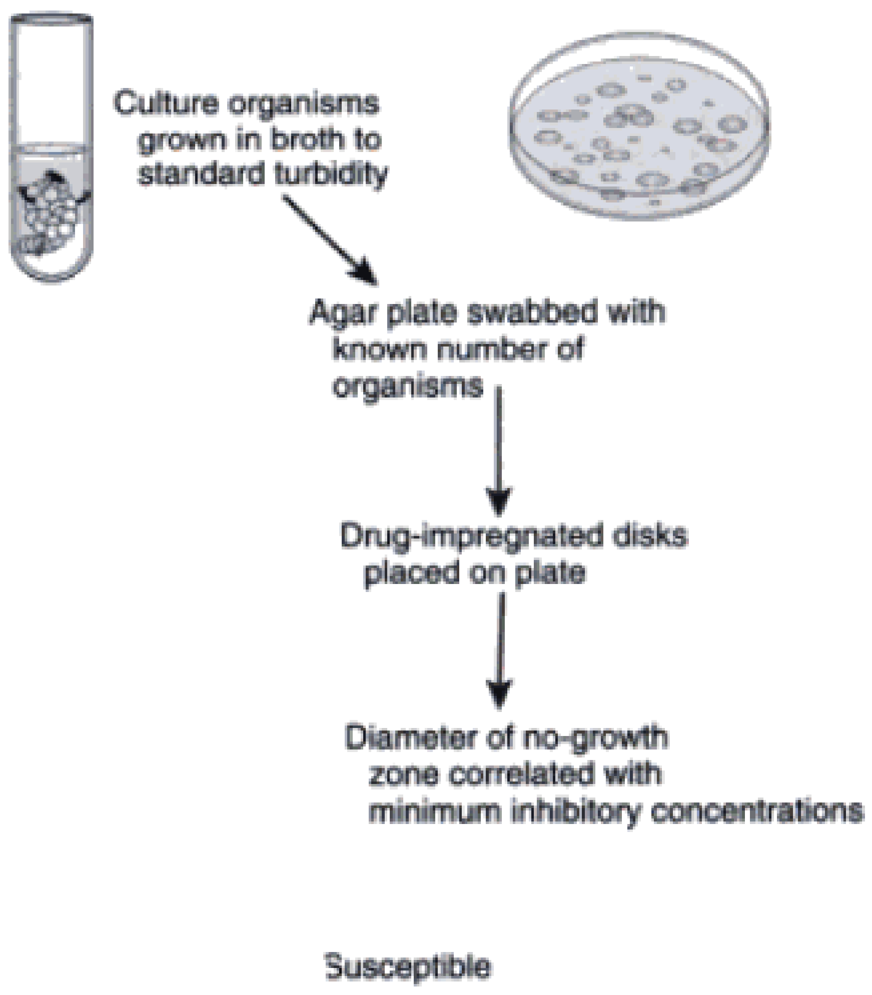

Culture organisms grown in broth to standard turbidity
Agar plate swabbed with known number of organisms
Drug-impregnated disks placed on plate
Diameter of no-growth zone correlated with minimum inhibitory concentrations
Susceptible

Figure 8–5. The agar plate method of culture and susceptibility testing. Drug diffusion from the disk results in concentrations that are higher close to the disk and gradually decrease as the diameter of the zone surrounding the disk increases. Resistant organisms can grow close to the disk despite high drug concentrations in the agar, whereas susceptible organisms will be inhibited at a standard distance from the disk. Concentrations in the agar correlate with the minimum inhibitory concentration (MIC) of the drug.

8–6) (Amsterdam, 1996). Tubes of liquid media contain decreasing concentrations of drugs. The concentrations increase serially by half. The tubes are inoculated with a standard number of the infecting bacterial organisms. Microbial growth is allowed to continue for a standard time, after which each tube is observed for evidence of growth. The tube with the lowest concentration of drug that exhibits no observable growth contains the MIC (in μg/mL) of the antimicrobial for the organism cultured from the patient (Neu, 1994; Amsterdam, 1996). The MIC provides a target concentration on which antimicrobial therapy can be based. A particular organism will be inhibited at a range of MICs (Table 8–4). Thus, the MIC of amikacin (or any other drug) for an *E. coli* is different for each strain of *E. coli*. The MIC_{90} and MIC_{50} of a drug reflect the MIC necessary to inhibit 90% and 50%, respectively, of the strains reported. For this statistic to be established by the National Committee for Clinical Laboratory Standards (NCCLS), an adequate number of organisms (at least 100) should be tested.

The tube dilution method can also provide information regarding the ability of a drug to kill (rather than simply inhibit) an organism. The minimum bactericidal concentration (MBC) is the smallest concentration of a drug that will kill the organism. It is determined by plating each tube that contained no visible evidence of growth. The smallest concentration that yields no growth when plated is the MBC. For drugs that are bactericidal (see later discussion), this concentration is very close (e.g., one tube dilution away) to the MIC.

Breakpoint MIC

The efficacy of an antimicrobial depends on the relationship between drug concentration and the MIC of the drug (i.e., the minimum concentration that will inhibit the in vitro growth of the organism). The drug concentration at the site of infection presumably must at least equal the MIC in order to be effective (Fig. 8–7). Thus, the plasma drug concentrations (PDC) must be sufficiently high to ensure adequate tissue concentration. Ideally, the concentration at the tissue site would be sufficient to achieve the MBC. This implies that the efficacy of an antimicrobial cannot be solely based on in vitro testing. Rather, efficacy must also take into account the clinical pharmacology of the drugs to be used to treat the infection. Drug absorption, distribution, and elimination become pertinent, as do drug toxicity and host factors at the site of infection.

The "breakpoint MIC" takes into account the clinical pharmacology of a drug as well as the susceptibility of the organism to the drug. The breakpoint MIC might best be understood as the approximating drug concentration that can reasonably be achieved safely in the plasma using the clinically accepted dose and route (Wiedemann, 1995). The MIC breakpoint for a drug, or the upper limit for susceptibility, is established by the NCCLS. Although it provides a basis for interpretation of MIC, it must meet several criteria. The breakpoint MIC must be lower than the concentration of the drug achieved in blood when administered at clinically accepted doses and routes (see Fig. 8–7). The MIC breakpoint should be within the limits of microorganisms with similar susceptibilities. Finally, the MIC breakpoint must be clinically relevant, that is, the microorganisms defined as susceptible should respond clinically to the drug, and in vitro data must correlate adequately with in vivo findings (Wiedemann and Atkinson, 1996).

Whereas the MIC is specific to the organism cultured and the drug of interest, the breakpoint MIC is specific to the host and drug. Thus, the breakpoint MIC of a drug is generally the same for any organism (Fig. 8–8 and Table 8–5). An exception is sometimes made for organisms that are particularly resistant to some drugs (e.g., *Staphylococcus* species that produce β-lactamases, increasing resistance to penicillins). In such cases, two different MIC breakpoints might be offered (see Table 8–4). For all organisms, both a "susceptible" breakpoint (below which the organism is considered susceptible) and a "resistant"

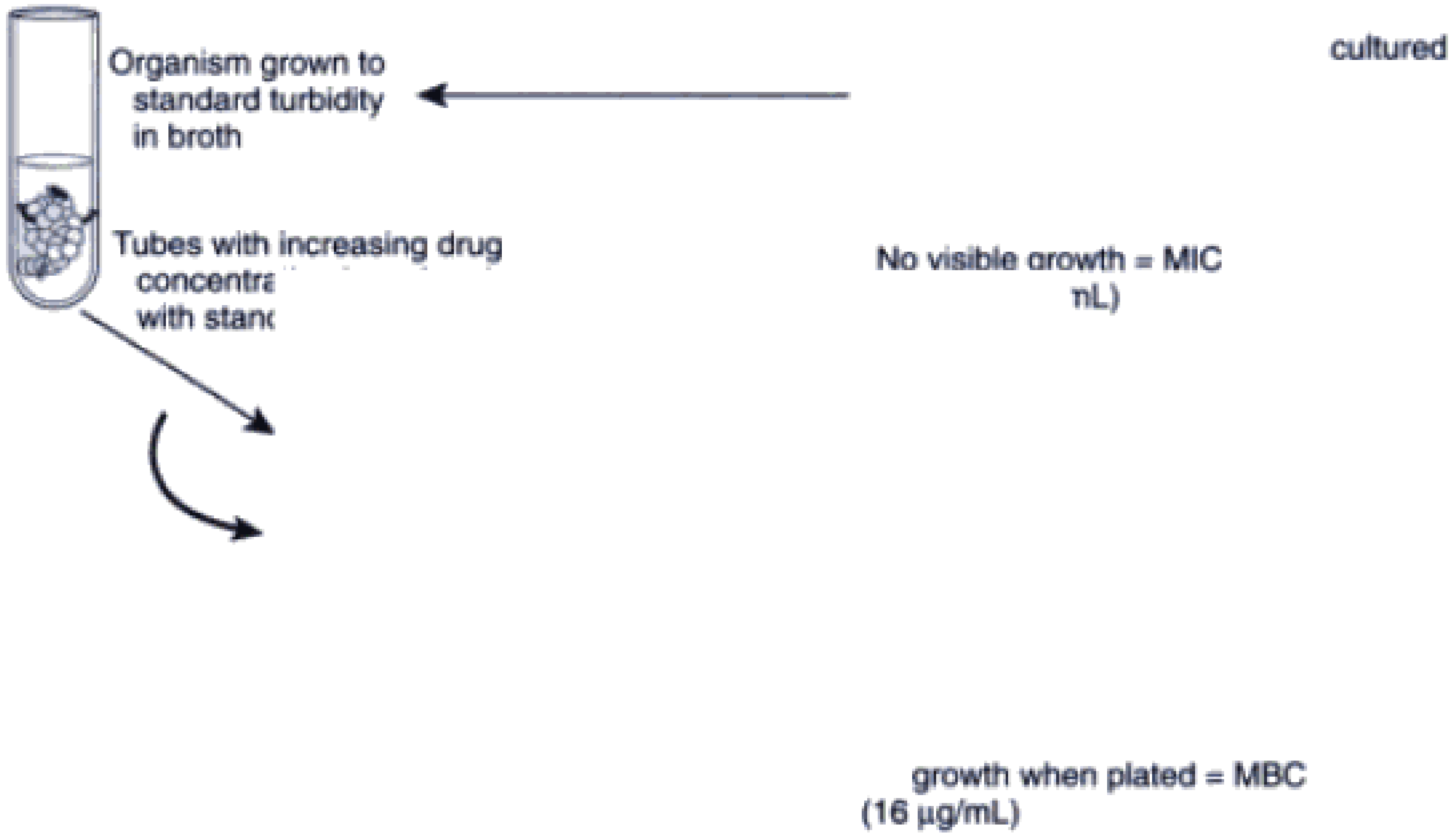

cultured
Organism grown to standard turbidity in broth
Tubes with increasing drug concentra
with stanc
No visible growth = MIC
nL)
growth when plated = MBC
(16 μg/mL)

Figure 8–6. The tube dilution method of susceptibility testing provides a target drug concentration. Tubes containing serially increasing concentrations of drug are inoculated with a standard amount of the bacterial organism. At the proper time, tubes are observed for evidence of growth. The first tube (i.e., that with the lowest concentration) that shows no evidence of growth contains the minimum inhibitory concentration (MIC) of the drug. If the tubes are plated on agar, the tube that yielded no bacterial growth contains the minimum bactericidal concentration (MBC). For bactericidal drugs, the MIC is close (one or two tube dilutions) to the MBC. The MIC can be used to evaluate relative drug efficacy and development of resistance and to calculate dosing regimens.

Table 8–4. Minimum Inhibitory Concentrations (MIC_{50} and MIC_{90} [μg/mL]) of Selected Antimicrobials for Selected Organisms*

	Staphylococcus aureus		*Escherichia coli*		*Klebsiella pneumoniae*		*Proteus mirabilis*		*Serratia marcescens*		*Pseudomonas aeruginosa*	
Drug	50	90	50	90	50	90	50	90	50	90	50	90
Amikacin	1–32	2–≥64	0.5–2	1–2	0.5–2	1–2	1–2	2–4	1–4	4–16	0.5–64	2–64
Amoxicillin alone	1–4	4–64	0.5–32	≥8–2048	≥16–128	≥16–1024	≥0.5–2	≥0.5–≥128	≥32–128	≥32–512	2048	2048
Amoxicillin with clavulanic acid	0.06–≥16	0.25–≥16	4–16	8–16	2–16	8–32	1	1–8	≥16–128	≥16–256	32–512	32–512
Ampicillin	0.125–2	0.125–64	8–512	8–512	64	≥512†	≥2	≥2	≥512	≥512†	—	—
Cefazolin	2–≥32	4–32	1–8	2–≥128	0.4–2	4–32	4–8	8–16	512	512	—	—
Cefotaxime	1–≥32	2–64	0.06–0.125	0.06–16	0.03–0.06	0.125	0.06–0.25 or less	0.03–0.125 or less	0.25–0.5	4–32	16	≥32–64
Cefoxitin	4–≥16	≥16	2	4	2	8	2	4	32	64	—	—
Ceftiofur												
Cephalexin	2–≥128	4–≥128	4–8	8–32	4–8	8–32	2–≥32	8–64	32–256	≥32–256	≥128–≥2048	≥128–≥2048
Cephalothin	16	32	4	8	1	16	—	—	≥256	≥256	—	—
Chloramphenicol	4	8	4	128	4	512	8	64	16	512	—	—
Ciprofloxacin	0.125–1	0.25–4	0.0075–0.06	≥0.0075–0.25	≥0.0075–0.03	0.03–0.25	≥0.004–0.125	0.03–0.25	0.03–0.125	0.125–8	≤0.0075–125	0.012–1
Clindamycin	0.125–≥128	25–≥128	—	—	—	—	—	—	—	—	—	—
Doxycycline	0.25	8	2	64	4	32	32	32	8	32	16	32
Enrofloxacin	0.3–1	0.25		0.06	0.03–0.5		0.03–0.5†	0.25	0.01–1	—		—
Gentamicin	0.125–0.25	—	0.25–1	0.5–16	0.06–≥16	0.05–≥16	0.25–2	0.5–4	0.5–2	8–32	0.5–4	1–≥32
Imipenem/cilastin	≤0.015–16	0.06–≥16	0.125–0.5	0.125–0.5	0.125–0.25	0.25–0.5	0.25–4	1–4	0.5–1	2	1–4	2–8
Kanamycin	0.5	2	1	16	1	32	0.5	8	2	128	—	—
Penicillin G	0.25–16	0.5–32	—	—	—	—	—	—	—	—	—	—
Piperacillin	1–256	4–1024	0.5–1	1–≥1024	2–4	16–128	0.25–64	2–≥1024	2–4	8–256	4–64	16–512
Ticarcillin alone	—	—	4	512	128	512	1	8	8	512	25–≥128	100–512
Ticarcillin with clavulanic acid	1	2	2	32	2	32	0.5	0.5	8	128	16	512
Tobramycin	0.125	0.25	0.25	0.5	0.25	1	0.25	0.5	2	32	0.125–1	4–6
Vancomycin	1–0.5	1–2	—	—	—	—	—	—	—	—	—	—

*MIC information extrapolated from literature on humans including Amsterdam 1996. MIC_{50} and MIC_{90} are the MICs necessary to inhibit 50% and 90%, respectively, of the organisms tested. Ranges reflect different MICs from the various reports (from Table 8–3). Data can be compared with those for organisms cultured from patients in order to evaluate the relative susceptibility of that organism to organisms reported in the literature.

†*Klebsiella* sp. or *Serratia* sp.

Other MIC_{50} for enrofloxacin include 0.5 μg/mL *(Bordetella)*, 0.25 μg/mL *(Salmonella)* and 0.5 μg *(Mycoplasma* sp). The MIC_{90} data for enrofloxacin were reported by NCCLS in 1999.

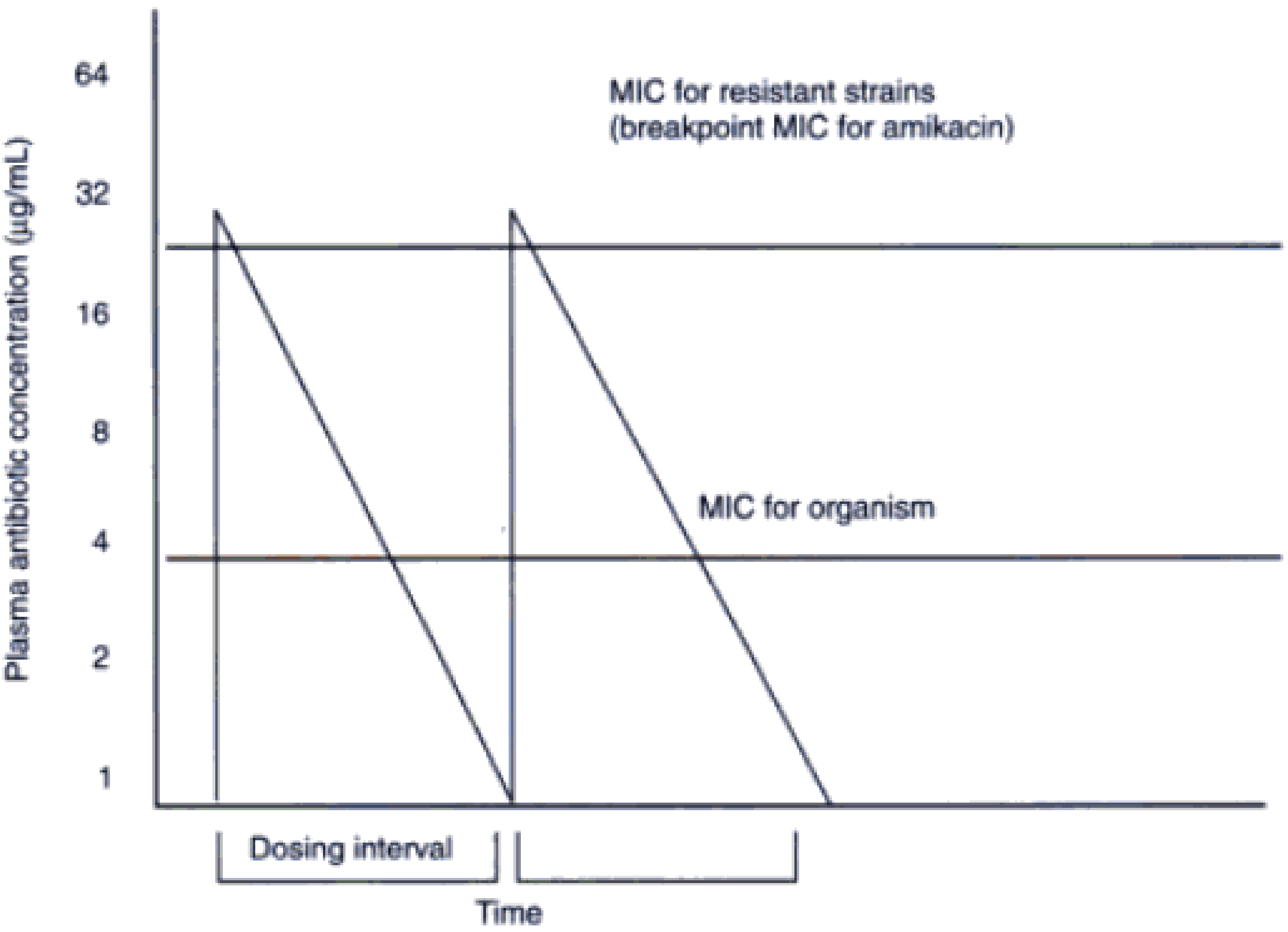
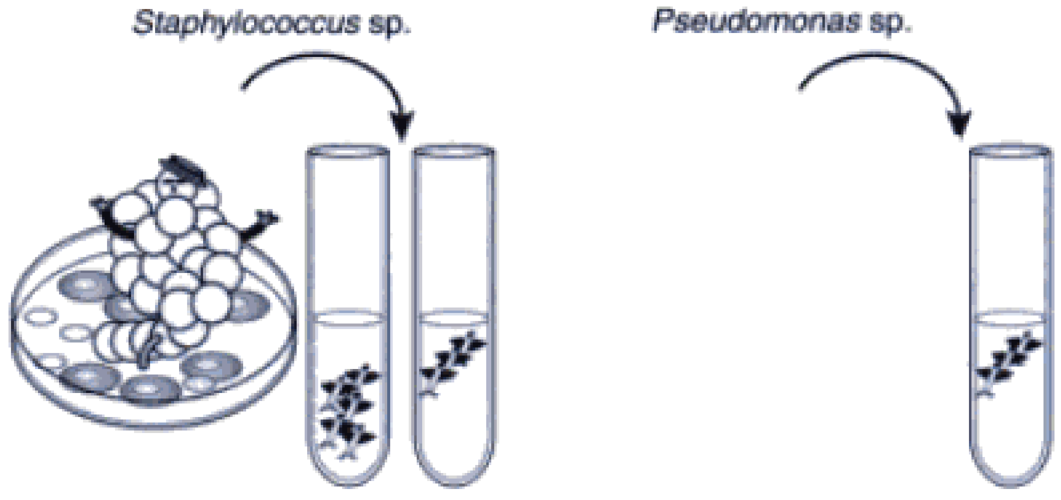


Figure 8–7. Ideally, plasma and tissue drug concentrations surpass the minimum inhibitory concentration (MIC) of the organism and for many drugs stay above the MIC of the organism throughout most of the dosing interval.

breakpoint (above which the organisms are resistant) are reported for a drug (see Table 8–5), with a "gray" zone of intermediate susceptibility often occurring between the two breakpoint MICs (see Table 8–5). Care should be taken when the MIC of the organism approaches the resistant MIC, unless the site of infection is one where the drug is likely to concentrate in active form. Breakpoint MIC data generally can be obtained from sources such as the *Physician's Desk Reference* (if the drug is approved for humans), the professional flexible labels on newer animal drugs, and the laboratory that provides the microbiologic data. The laboratory that will provide the culture and susceptibility data should be contacted regarding the breakpoint values used in their tests. Drugs should be selected such that the dosing regimen will result in a PDC that sufficiently surpasses the MIC but remains safely below a toxic concentration.

For susceptible organisms that have MICs that are gen-


Staphylococcus sp.
Pseudomonas sp.

Amikacin	(>64)	S	2	S	4
Amoxicillin	(≥32)	S	8	R	>16
Amox/ clavulanic acid	(≥32)	S	4	R	>16
Cephalothin	(≥32)	S	2	R	>16
Enrofloxacin	(≥4)	S	0.25	S	1
Gentamicin	(≥16)	S	4	R	>16
Penicillin G	(≥16)	R	16	R	>16
Trimethoprim-sulfamethoxazole	(≥4)	S	1	R	>16

Figure 8–8. The relative efficacy of antibiotics to which an organism is susceptible can be evaluated by comparing the minimum inhibitory concentration of the organism to the breakpoint of the drug (number in parentheses reflects the resistant breakpoint for each drug in μg/mL; see Table 8–5). For example, for *Staphylococcus*, the minimum inhibitory concentration for amikacin is 1/32 the concentration of the breakpoint (or four tube dilutions away), whereas that for gentamicin is 1/4 of the breakpoint. Although both are considered susceptible, amikacin presumably would be more effective. When comparing *Staphylococcus* with *Pseudomonas*, the *Staphylococcus* should be easier to inhibit with any of the drugs (except penicillin G). All values (concentrations) are in micrograms per milliliter. S = susceptible; R = resistant; I = intermediate.

Table 8–5. Pharmacokinetic Data and Interpretive Standards for Disk Diffusion and Equivalent Minimum Inhibitory Concentration (MIC) Breakpoints for Selected Antimicrobials

Drug	Volume Distribution (L/kg)	Half-Life (Hour)	C_{max} (µg/mL)/ Dose (mg/kg)*	Breakpoint (µg/mL) Susceptible	Breakpoint MIC (µg/mL) Resistant
Amikacin	0.23 (D) 0.18–0.38 0.14(C)	1	65/20 (IV) 14/10 (IM)	≤16	≥64
Amoxicillin	0.2 (D)	1–1.5	13/20 (IV) 6–11 (PO) 7/11 (SC, D) 10 (SC, C)	≤16§ ≤0.25‖	≥32 ≥0.5
Amoxicillin with clavulanic acid	0.2	1–1.5	13/20 (IV) 6/11 (PO) 7/11 (SC, D) 10/15 (SC, C)	≤4§ ≤16§	≥8 ≥32
Ampicillin	0.2–0.4 (D) 0.2 (C)	0.5–1.5	50/20 (IV) 14/12 (SC) 7/6.6 (SC) 10/30 (PO) 3/10 (PO)	≤8§ ≤0.25‖	≥32 ≥0.5
Carbenicillin	0.19	0.25			
Cefaclor			24.5/25 (PO, D)¶ 20/44 (PO, D)¶		
Cefamandole			9.4/10.7 (IV, D)¶		
Cefadroxil			10.5/11 (PO, D)¶ 16.3/22 (PO, D)¶ 21/44 (PO, D)¶		
Cefazolin**	0.3–0.7	0.75–1.4	45/15 (IV) 90/30 (IV) 25/15 (SC) 50/30 (SC)	≤8	≥32
Cefotaxime††	0.48 (D) 0.18 (C)	0.75 (D) 1 (C)	41/50 (IV, IM, D)¶ 35/10 (IV, D)¶	≤8	≥64
Cefotetan††	0.25	0.9	43/20 (IV, D)¶		—
Cefoxitin‡‡	—	—	20/60 (IV) 10/30 (IV) 20/30 (SC) 15/10 (SC)	≤8	≥32
Ceftazidime††	0.22	49	49/20 (IV)¶		≥32
Ceftiofur††	—	—	—	—	—
Ceftizoxime††	0.26	1	50/20 (IV, D)		≥32
Ceftriaxone††	0.24	0.85	45/20 (IV)¶		≥64
Cefuroxime			70/60 (IM, D)¶		
Cephalexin**	0.23	—	20/22 (PO) 28/30 (PO)	≤8	≥32
Cephalothin**	0.43	0.7–0.85	9.3/10 (IM)¶ 35/20 (IV) 45/40 (IV) 22/20 (SC) 30/40 (SC)	≤8	≥32
Cephapirin**	0.32	0.5	26.9/30 (IV)¶		—
Cephradine			39/50 (PO)¶		
Chloramphenicol	1.77 (D) 2.36 (C)	6–8 (D) 5.1 (C)	8.5/33 (PO, D) 15/33 (SC, D) 10/55 (PO, D) 12/15 (tablet, C) 10/15 (solution, PO, C)	≤8	≥32
Ciprofloxacin	—	—	—		≥4
Clindamycin	—	—	5/11 (PO, D) 2/5.5 (PO, D) 11/15 (PO, C) 9/11 (PO, C)	≤0.5	≥4
Cloxacillin	0.2	0.5			
Dicloxacillin	0.2	0.7			
Doxycycline	0.93–1.5 (D) 0.34(C)	7–10 (D) 4.6 (C)	5/5 (PO, D) 3/2.5 (PO, D) 6/5 (PO, C) 3/2.5 (PO, C)	≤4	≥16

Table 8–5. Pharmacokinetic Data and Interpretive Standards for Disk Diffusion and Equivalent Minimum Inhibitory Concentration (MIC) Breakpoints for Selected Antimicrobials *Continued*

Drug	Volume Distribution (L/kg)	Half-Life (Hour)	C_{max} (μg/mL)/ Dose (mg/kg)*	Breakpoint (μg/mL) Susceptible	Breakpoint MIC (μg/mL) Resistant
Enrofloxacin	2.6	0.92 (2.5)	2/5 (PO, D)	≤1	≥4
		2.02 (5)	1/2.5 (PO, D)		
			2.5/5 (PO, C)		
			1.3/2.5 (PO, C)		
Erythromycin			3.5/20 (PO)	≤0.5	≥8
Gentamicin	0.25–0.34 (D)	0.87–1.36 (D)	44/8 (IV)¶	≤4	≥16
	0.14–0.2 (C)	1–1.36 (C)	27/4 (IV)¶		
			28/10 (IV, D)		
			7.5/4.4 (IM, D)		
			6/2.2 (IV, D)		
			28/10 (IV, C)		
			4/2/2 (IM, C)		
Imipenem/cilastin	8?	—	180/30 (IV)	≤4	≥16
			65/10 (IV)		
Kanamycin	0.23–0.28	0.75–1	—		≥16
Lincomycin			1.2/22 (PO)	≤0.5	≥4
			1.0/15 (PO)		
Metronidazole	0.95	4.3	60/44 (IV)		—
Minocycline	2 (D)	7–7.3 (D)			
Oxacillin	0.3 (D)		4.0/40 (PO)	≤2	≥4
			3.0/30 (PO)		
Oxytetracycline	2 (D)	6 (D)			
Penicillin G	0.16	0.5	30/20,000 U/kg (IV)	≤8§	≥16
			14/22,000 U/kg (SC)	≤0.12‖	≥0.25
Piperacillin	—	—	250/50 (IV)	≤16§	≥128
			125/25 (IV)	≤64‖	≥128
Sulfadiazine (SDZ)/trimethoprim (TMP)	1.49 (TMP)	2.5 (TMP)		≤2	≥4
	1.02 (SDZ)	9.8 (SDZ)			
Sulfamethazine	0.5–0.6 (D)	16–17 (D)			
Tetracycline			9/20 (PO, D)	≤4	≥16
			7/13.75 (PO, D)		
Ticarcillin	0.34 (D)	1	200/100 (IV)		≥258
			80–40 (IV)		≥128
Ticarcillin with clavulanic acid	—	—	200/100 (IV)		≥256/4
			80/40 (IV)		≥128
Vancomycin	—	—	—		≥14

*C_{max} refers to the maximum serum concentration obtained at the dose given by the route in parentheses (IV = intravenous; IM = intramuscular; SC = subcutaneous; PO = oral). Data refer to both cat and dog unless indicated otherwise (D = dog; C = cat). The C_{max} following a different dose will change in proportion to the difference in the dose administered compared with the dose listed in the table. For example, a 20 mg/kg IV dose of amikacin resulted in a C_{max} of 40 μg/mL. If a patient is given 10 mg/kg IV amikacin, a C_{max} that is approximately 50% less than that noted in the table should occur (i.e., about 20 μg/mL. This information can then be used to evaluate the appropriate dose necessary to achieve a desired plasma drug (and thus tissue drug) concentration. The data are most useful when an MIC is available for the target organism. Other doses are available in Appendix 8.

§When testing gram-negative enteric organisms.

‖When testing staphylococcal organisms.

¶From Caprile, 1988.

**First generation.

††Third generation.

‡‡Second generation.

(D) = Dog.

(C) = Cat.

Data are from Aucoin (1993) and Caprile (1988¶).

erally achievable in serum (i.e., below the breakpoint) with the recommended dosing regimen, the use of the drug may be appropriate. It would, however, be inappropriate to ignore other considerations, most notably host factors and their impact on drug efficacy, as well as characteristics of the drug itself and its ability to reach the site of infection in active form. Thus, MIC data are one of many tools that should be used to facilitate antimicrobial therapy.

Organisms that are resistant to a drug are not readily amenable to treatment with that drug because their growth will not be inhibited at the breakpoint MIC. Indiscriminate dose increases to surpass the MIC or to achieve the MBC of a drug intended to treat a particular organism is inappropriate. Additionally, the risk of toxicity to the drug may outweigh the potential benefits of therapy with this drug. Many organism and drug combinations exhibit a paradoxical effect when drug concentrations exceed the MBC. As drug concentrations increase, the killing effect of the drug decreases, probably because of impaired protein synthesis. Impaired synthesis inhibits growth of the organism and renders it less susceptible to the killing effect. Additionally, just because the MIC of an organism is not acheived in tissues does not mean that a therapeutic benefit will not be realized. For some drug and organism combinations, impaired antimicrobial activity (growth, adherence, toxin production, or susceptibility to phagocytic actions) occurs at subtherapeutic concentrations (Amsterdam, 1996).

Note that the MIC breakpoint is based on a single dose. Information regarding susceptibility based on that dose is not likely to apply to a higher or lower dose. For example, the MIC breakpoint for enrofloxacin is based on the dose of 2.5 mg/kg, but the new flexible label extends to 20 mg/kg (Boothe, 1999a). Thus, susceptibility data for enrofloxacin may grossly underestimate efficacy at the higher dose unless new breakpoints recently established by the NCCLS to reflect the flexible label enrofloxacin are being used by the testing laboratory (see Chapter 9 and Table 8–5). Likewise, as aminoglycoside therapy once daily becomes the norm rather than the exception, susceptibility data based on older 8- or 12-hour doses may underestimate efficacy of 24-hour (higher) doses. Note that all drugs do not have NCCLS guidelines. Often a lab will select a prototypical drug to represent a drug class. However, assuming similar patterns of efficacy among drugs in the same class may not be appropriate in many cases.

Evaluation of the Relative Efficacy of Antimicrobials

The relative efficacy of antimicrobials against a specific organism cannot be determined based on absolute MICs, which will vary among the drugs (see Table 8–5). For example, *Pseudomonas* in Figure 8–8 is not more susceptible to enrofloxacin with an MIC of 1 μg/mL compared with amikacin with an MIC of 4 μg/mL. Minimum inhibitory concentrations among the various drugs differ in the same organism for a number of reasons, for example, molecular weight (one drug is simply heavier than another), differences in drug penetrability into the organism, and mechanisms of antimicrobial action (Levison and Bush, 1989). MICs for different drugs must be compared in the context of the breakpoint for each drug (how far from the breakpoint MIC is the MIC of the drug for the organism?) For problematic infections, more ideally, the MIC of the organism might be compared to tissue concentrations of drug in the target tissue in order for relative efficacy to be compared among drugs. With certain caveats, the MIC data that accompany culture data can be used several ways to enhance therapeutic success with an antimicrobial:

1. The relative susceptibility of the organism cultured from the patient to a particular drug can be compared with the susceptibility of the organisms reported in the literature (e.g., MIC_{90}) (i.e., how susceptible is this *E. coli* compared with another *E. coli* to amoxicillin?).
2. The relative susceptibility of the organism can be compared among each drug listed in the susceptibility report (i.e., is this *E. coli* more susceptible to amoxicillin or gentamicin?).
3. MIC data can indicate an increasing pattern of resistance (i.e., is this *E. coli* as susceptible to amoxicillin on this culture as it was when cultured 2 weeks ago?).
4. A dose of a toxic or expensive drug can be estimated based on the distance between the MIC of the organism (or the reported MIC_{90} if the identity but not the MIC of the infecting organism is known) or it can be calculated for the particular organisms (Thompson, 1989; Brown, 1987; Schentag et al., 1991). This exercise can be used to maximize efficacy (e.g., with aminoglycosides), to minimize toxicity, and to minimize antimicrobial expense by establishing a minimum yet potentially effective dose of drug (see later discussion of enhancement of antimicrobial efficacy).

Often a susceptibility report will reveal an organism to be susceptible to several drugs. The decision regarding which one to use can be facilitated by comparison of the relative susceptibility to each drug. If a *Staphylococcus* exhibited an MIC of 8 μg/mL to both gentamicin (MIC breakpoint 16 μg/mL) and amikacin (MIC breakpoint 64 μg/mL), amikacin would be the better choice because the distance between the MIC and the breakpoint is much greater for amikacin than for gentamicin. Establishing relative efficacy among drugs in the same class is facilitated by the assumption that the disposition and toxicity of the drugs in the class will be the same, and thus host and drug effects will be similar. Comparison of the relative efficacy among drugs of different classes is more difficult because of differences in drug disposition and susceptibility to environmental factors at the site. However, the same approach can be used but the selection further modified by host and drug considerations.

The relationship between the MIC or MIC_{90} of an infecting organism to the breakpoint MIC (or, if not available, to peak PDC) can also be used to modify a dosing regimen. The closer the MIC is to the PDC, the higher the dose of the antimicrobial should be to facilitate adequate drug concentrations at the infection site.

The difference between an MIC of 16 versus 32 mg/mL may seem quite large (particularly in the context of PDCs), but in fact it represents only one tube dilution difference. This observation exemplifies one of the hazards of overinterpreting susceptibility data. If the MIC of an organism is close to the breakpoint, variability in interpretation may result in an "S" (sensitive) or "MS" (medium or intermediate susceptibility) designation by one laboratory but an "R" (resistant) by another. Thus, drugs to which an organism is MS (or the MIC is close to but below the breakpoint) should be avoided, with one exception. The exception occurs when the drug can be concentrated at the site of infection well beyond the MIC measured in the in vitro test, which reflects MIC breakpoints established in plasma. The best example of such a situation is the use of a drug that is renally eliminated (biliary eliminated) to treat a urinary tract (biliary tract) infection. Concentration of selected drugs by white blood cells (e.g., fluorinated quinolones, macrolides) may also result in a much higher drug concentration at the tissue site than in the plasma.

The MIC of an organism may differ with subsequent infections in the same patient. An MIC may change during the course of infection in a patient; an increase may simply be a difference in interpretation (especially if the difference is only one tube dilution), but it might also be interpreted as the development of resistance against a drug. In such instances, antimicrobial therapy might be altered by addition of another drug or a change to a more effective drug.

For polymicrobial infections, the MIC of a drug is likely to be different for each infecting organism (see Table 8–5). An organism with a lower MIC for a given drug should be easier to inhibit than an organism with a higher MIC for the same drug.

As can be seen by the previous discussion, the tube dilution method of susceptibility testing can provide quite a bit of information to facilitate antimicrobial selection. Automated, rapid instumentated methods are becoming increasingly available to practitioners interested in susceptibility testing. Ideally, the concentrations studied in liquid media should include a wide range, approximating the range of MICs established for the organisms (see Table 8–5). Concentrations tested should ideally include and exceed by at least one dilution step the highest range concentrations in biologic fluids (Amsterdam, 1996). Unfortunately, some of the new automated systems do not truly test for susceptibility. Rather, they test over a very short range of concentrations that are close to the breakpoint. Such tests are more indicative of "resistance" rather than susceptibility and limit the ability of the clinician to discriminate among the effective antimicrobials. For problem cases, laboratories that provide information over a broad range of MICs should be sought. Additionally, the MIC range tested (and the breakpoint MIC) is based on the lower labeled dose (e.g., 2.5 mg/kg for enrofloxacin). The wider the dosing range provided on flexible labels, the more likely the susceptibility data will underestimate susceptibility (when the drug is used at doses higher than that on which the breakpoint is based). Currently, of the veterinary fluorinated quinolones, only enrofloxacin has NCLLS established breakpoint MIC, which was recently modified to reflect the broad dosing range of this drug.

Despite the importance of culture and susceptibility information, clinicians must remember that the information reflects in vitro testing (Amsterdam, 1996; Acar and Goldstein, 1996). Results can be misleading even with ideal culture conditions. The controlled system of the culture does not occur in the patient; culture results must be interpreted in the context of potential host factors that can alter concentrations of active drug at the tissue site.

Relationship between Minimum Inhibitory Concentration, Plasma Drug Concentration, Tissue Concentration, and Drug Efficacy

Postantibiotic Effects The efficacies of antimicrobials are based on the relationship of MIC to PDC. Although the concentrations of a drug may equal the MIC in plasma, concentrations may be much lower and, possibly nondetectable by the end of the dosing regimen. Yet antimicrobial efficacy may not be impaired. Persistence of the antimicrobial effect after brief exposure to (or the lack of detectable concentrations of) an antimicrobial has been termed the *postantibiotic effect* (PAE) (Levison and Bush, 1989; Craig and Vogelman, 1987; Craig and Gudmundsson, 1996; Spivey, 1992).

The PAE is therapeutically important for some antimicrobials against some organisms. The duration of the PAE differs among the bacterial organisms for each drug. For some organisms, the duration of the PAE depends on the relationship between PDC and MIC. For example, the PAE and efficacy for aminoglycosides are maximized by a large PDC/MIC or *inhibitory quotient* (perhaps best defined by the ratio of PDC/MIC necessary to inhibit the organism) and then a drug-free period (i.e., a long interval between doses) (Fig. 8–9) (Schentag, 1991; John, 1988; Vanhaeverbeek et al., 1993; Moore et al., 1987; Carbon, 1992). In contrast, the efficacy of many β-lactams is enhanced by continuous drug administration or shorter dosing intervals. The PAE can impact the dosing interval for some antimicrobials (Amsterdam, 1996; Thompson, 1989; Craig and Gudmundsson, 1996). Presumably, the dosing interval should equal the time for which PDC are above the MIC plus the duration of the PAE (Brown, 1987). The PAE may be absent for some organisms or some patients (e.g., some immunocompromised patients) (Levison and Bush, 1989). In addition, PAEs vary with each drug and each organism.

Bactericidal Versus Bacteriostatic Antimicrobials Organisms whose growth is merely inhibited by "bacteriostatic" drugs must be killed by host defenses. In contrast, organisms subjected to "bactericidal" drugs are killed and host defenses, while helpful, are not necessary (Table 8–6) (Neu, 1994). The need for a bactericidal drug for selected patients is well appreciated. Patients that are immunodeficient and, in particular, granulocytopenic are dependent on bactericidal activity for eradication of infection (Schimpff et al., 1989). Effective treatment of infections in an immunoincompetent environment also depends on bactericidal antimicrobial activity. These environments include but are not limited to septicemia, meningitis, valvular endocarditis, and osteomyelitis (Neu, 1994). For a bactericidal drug, the MIC is very close to the concentration necessary to kill the organism, that is, the MBC (Neu, 1994; Amsterdam, 1996). The distinction between a bactericidal and a bacteriostatic drug, however, depends on the concentration to which the bacteria is exposed. A bactericidal drug can be easily rendered nonbactericidal if concentrations sufficient to kill the organism are not reached at the site of infection. In contrast, drugs are concentrated in some tissues, and even a static drug might become bactericidal in selected instances.

Careful consideration must be given to factors that can reduce concentrations of active drug at the site of infection (Neu, 1994; Brumbaugh, 1990; Korzeniowski, 1989). One method to facilitate achievement of adequate concentrations of drug at the site of infection is the use of a "therapeutic factor" in calculating a target PDC. The therapeutic factor helps compensate for some of the differences that occur between culture (MIC) data and patient conditions. In general, the target PDC of a drug in a patient is the MIC of the drug multiplied by a therapeutic factor of 4 to 10 (Fig. 8–10) (Neu, 1994; John, 1988; Vanhaeverbeek et al., 1993; Maller et al., 1993). The more virulent the organism, the more immunocompromised the patient, the more serious or complicated the infection, or the more difficult it is for a particular drug to penetrate to the site of infection, the greater the desired ratio of PDC/MIC (inhibitory quotient) and thus the therapeutic factor (Kapusnik et al., 1989). For example, in a granulocytopenic patient infected with *P. aeruginosa*, the target PDC for an aminoglycoside (a concentration-dependent drug) in the patient might be 8 to 10 times the MIC (i.e., an IQ of 8 to 10). Higher inhibitory quotients should also be targeted for

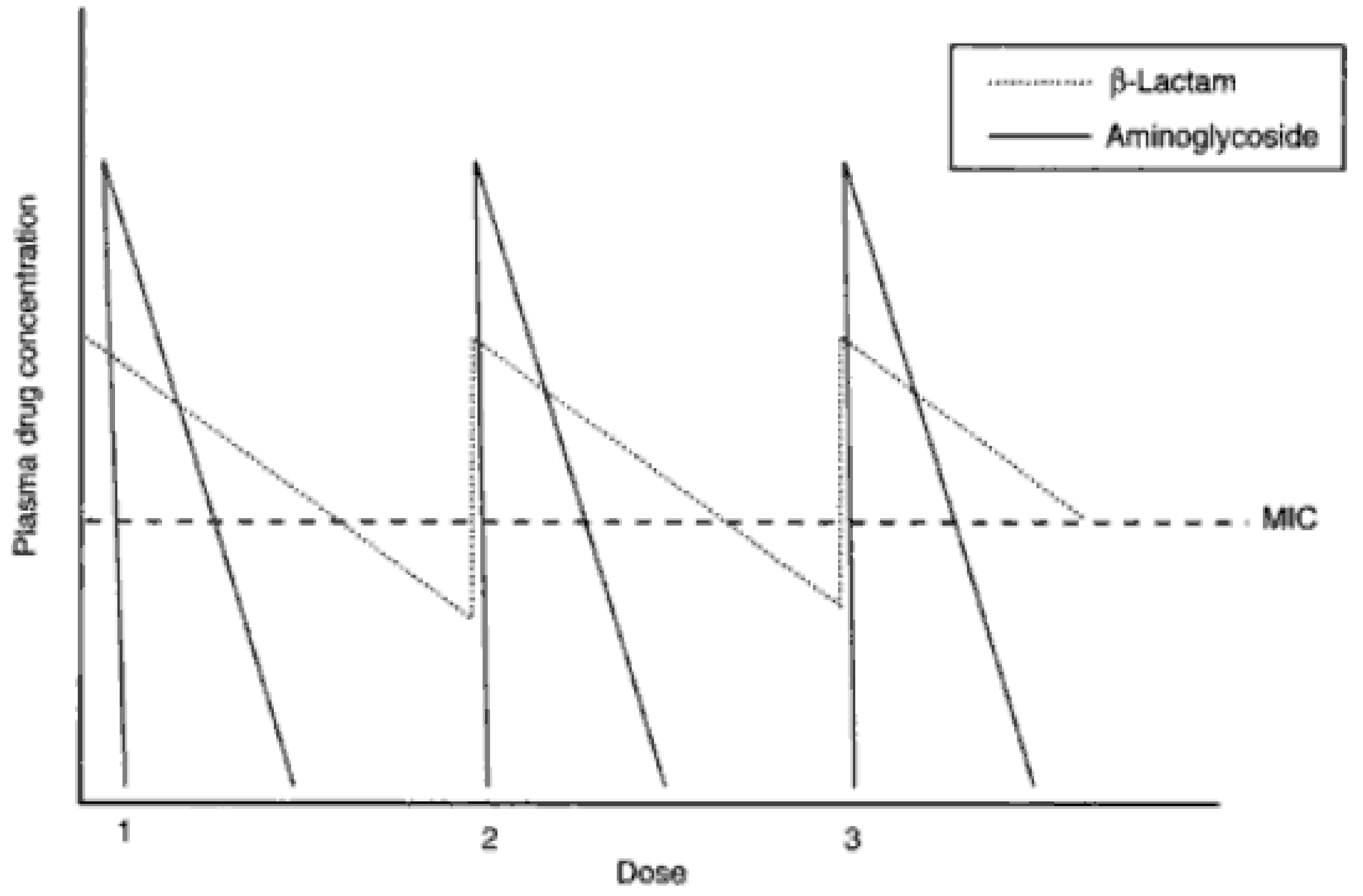


Figure 8–9. The relationship between plasma (tissue) drug concentration, and the minimum inhibitory concentration of the organism may determine drug efficacy. The efficacy of aminoglycosides depends on a high inhibitory quotient: Plasma drug concentrations must be maximized to ensure a high plasma drug concentration to minimum inhibitory concentration (MIC) ratio. In contrast, for β-lactams, efficacy is maximized by ensuring that plasma drug concentration remains above the minimum inhibitory concentration for most of the dosing interval. MIC = minimum inhibitory concentration.

infections in tissues that are difficult to penetrate. Indiscriminate use of a large therapeutic factor should be avoided so that the potential for toxic drug concentrations is minimized. In general, for toxic drugs ideally the MIC times the therapeutic factor should result in a PDC below the breakpoint MIC for that organism in order to remain safe. Thus, the closer an MIC of an organism is to the breakpoint MIC for the drug, the less "room" there is for error and the smaller the therapeutic factor. An exception can be made for drugs sufficiently safe that the breakpoint MIC can be surpassed. In such instances, a dose higher than that recommended on the label can be used.

The relationships between PDC, MIC, therapeutic efficacy, and the PAE vary according to the drug (Schentag, 1991; Vogelman et al., 1988; Schentag et al., 1991). This variability can impact the dosing regimen for a drug as is exemplified by comparison of β-lactam with aminoglycoside antimicrobials. Although the efficacy for aminoglycosides and the fluorinated quinolones is concentration or dose dependent (i.e., maximizing the inhibitory quotient) (John, 1988; Carbon, 1992; Korzeniowski, 1989; Maller et al., 1993; Nördstrom et al., 1990; Powell et al., 1983; Blaser, 1991), the efficacy for β-lactam antimicrobials and "bacteriostatic" drugs is time dependent (i.e., efficacy is enhanced if PDC remains above the MIC for most of the dosing interval) (see Fig. 8–9) (Schentag, 1991; Carbon, 1992). Thus, a dose that is too low is particularly detrimental with aminoglycoside or fluorinated quinolone therapy, but prolongation of the dosing interval should be avoided for β-lactams. For example, in a mouse model of *E. coli* peritonitis, the antibacterial efficacy of ciprofloxacin, but not imipenem, was improved by doubling the dose. The efficacy of fluorinated quinolones appears to be dose related but may also be time related (Nitsche et al., 1996; Wetzstein, 1994; Marchbanks et al., 1993). The optimal relationship between PDC and MIC and the parameter that best predicts antimicrobial efficacy (e.g., peak PDC; the ratio of area under the drug concentration vs. time curve to the organism's MIC; duration of PDC above MIC) have not been established definitively for all antimicrobials (Schentag et al., 1991; Schentag, 1991; Nitsche et al., 1996; Wetzstein, 1994). The clinical relevance of many

Table 8–6. Bactericidal and Bacteriostatic Drugs

Bactericidal	Bacteriostatic
Aminoglycosides	Chloramphenicol
β-Lactams	Clindamycin
Clindamycin	Lincosamides
Metronidazole	Macrolides
Quinolones	Sulfonamides
Rifampin	Tetracyclines
Sulfonamide/dipyrimidine (potentiated)	Tylosin
Vancomycin	

Target: *Pseudomonas aeruginosa*
Desired target: PDC 8 x MIC

Drug: Amikacin
MIC = 4 μg/mL Target PDC = 32 μg/mL Vd = 0.3 L/kg
Dose = 0.3 L/kg · 32 μg/mL = 10 mg/kg

Drug: Enrofloxacin
MIC = 1 μg/mL Target PDC = 8 μg/mL Vd = 3 L/kg
Dose = 3 L/kg · 8 μg/mL = 24 mg/kg

Figure 8–10. The dose of an antibiotic can be calculated if a minimum inhibitory concentration (MIC) is available (based on susceptibility data or reported MIC) and if the volume of distribution (Vd) of the drug is known. Note that for organisms with a high MIC that approaches but does not reach breakpoint, the dose of the antibiotic recommended may not result in a plasma drug concentration (PDC) that sufficiently surpasses the MIC (especially if a large therapeutic factor is desired). Tissue drug concentrations will be even less. Doses in such situations should be increased if safety is not a concern (μg/ml = mg/L).

Figure 8–11. *Nocardia* causes a marked inflammatory response by the host. Additionally, the organism causes secretion of calcium, resulting in the formation of "sulfur" granules that protect the organisms from drug penetrations.

of the studies focusing on the relationship between drug concentrations, MIC, and efficacy is lacking for many drugs (Levin and Karakusis, 1984). The studies, however, point out the importance of using appropriate dosing regimens to facilitate antimicrobial efficacy.

Microbial Factors Detrimental to Antimicrobial Efficacy Microbes can negatively affect antimicrobial therapy either by directly impairing antimicrobial efficacy (see later discussion of resistance to antimicrobials) or by adversely affecting host response to infection. Materials released from microbes facilitate invasion, impair cellular phagocytosis, and damage host tissues. Most staphylococci associated with canine pyoderma produce "slime," a material that facilitates bacterial adhesion to cells. Soluble mediators released by organisms (hemolysin, epidermolytic toxin, leukocidin) may damage host tissues or alter host response. Staphylococcal organisms contain protein A, which impairs antibody response, activates complement, and causes chemotaxis. *Nocardia* stimulates the formation of calcium-containing "sulfur granules" that impair drug penetration to the organisms (Fig. 8–11). *Pseudomonas* and other gram-negative organisms produce a glycocalix that protects the organism.

IDENTIFYING HOST FACTORS

Effects of Local Environment Detrimental to Drug Activity

Therapeutic failure can occur in a patient receiving antimicrobial therapy despite achieving targeted PDC because of microbial (previously discussed) and host factors that decrease the concentration of active drug at the site of infection (Brumbaugh, 1990). Changes in the health of the host can lead to changes in drug disposition that can result in lower than anticipated PDCs (see Chapter 2) (Thompson, 1989). The volume to which a drug is distributed can be affected by the fluid compartments, which vary with age, species, and hydration status. Distribution to target organs can be affected profoundly by cardiovascular responses, particularly in the shock patient. Elimination of the drug must be considered when selecting antimicrobials for the critical patient. Changes in glomerular filtration cause parallel changes in renal excretion of drugs. Serum creatinine concentrations should be used to modify doses or intervals of potentially toxic drugs that are excreted renally (see Chapter 2) (Lesar and Zaske, 1984). Likewise, severe changes in hepatic function may indicate selection of an antimicrobial drug not dependent on hepatic function for activation or excretion.

Host factors at the site of infection may profoundly alter drug efficacy and their presence may indicate the need for increasing the dose and/or interval, depending on the drug. The microenvironment of the site of infection profoundly impairs the activities of some antimicrobials (Table 8–7) (Neu, 1994; Brumbaugh, 1990). Purulent exudate presents an acidic, hyperosmolar, and hypoxic environment that impairs the efficacy of many antimicrobials (Fig. 8–12). Hemoglobin and degradative products of inflammation can bind antimicrobials (Bergan, 1981). Selected drugs, including aminoglycosides (and probably highly protein-bound drugs) are bound to and thus inactivated by proteinaceous debris that accumulates with inflammation. Some antimicrobials can inhibit neutrophil function. Accumulation of cellular debris associated with the inflammatory process can present a barrier to passive antibiotic distribution. The deposition of fibrous tissue at the infected site further impairs drug penetrance and distribution (Fig. 8–13).

Local pH becomes more acidic as degradative products such as lysosomes, nucleic acids, and other intracellular constituents from white blood cells accumulate. The efficacy of many antibiotics can subsequently be impaired. In humans, a pH ranging from 5.5 to 6.8 can adversely affect both host defenses and antimicrobial activity. White blood

Table 8–7. Effects of the Microenvironment on Antimicrobial Efficacy

Environmental Factor	Effect
Acidic pH	Penicillins inactivated at pH <6.0 Aminoglycosides and enrofloxacin more effective in alkaline pH
Hypertonicity/hyperosmolarity	Impaired efficacy of β-lactam antibiotics
Pus	Acidic pH Hypertonic Hyperosmolar Protein binding of selected drugs Binding to sediment (aminoglycosides)
Low O_2 tension	Aminoglycosides inactive Growth of organisms slowed → decreased efficacy of bactericidal drugs Impaired phagocytic activity of leukocytes
Large inoculum	Greater concentration of antimicrobial inactivating enzymes Greater concentration of drug molecules required
Leukocytes	Impaired chemotaxis, phagocytosis, metabolism

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Figure 8–12. The inflammatory response to bacterial pneumonia dilutes the drug, presents a barrier to passive diffusion, and may bind and thus inactivate the drug. Local pH and thus drug ionization may impair drug action, and generation of a decreased oxygen tension further decreases drug efficacy. (Photo courtesy of Bayer Animal Health.)

cell oxidative bursts and phagocytosis are diminished in the presence of a low pH. Some antibiotics are inactive at a low pH. Erythromycin loses all of its activity in a pH less than 7. Similar effects have been reported for β-lactam antibiotics. Although β-lactam antibiotics are weak acids and therefore less ionized in an acidic environment, they are destroyed in pH 6.0 or less. The activities of cefoxitin, piperacillin, and imipenem are significantly less at pH 6.0 than at pH 6.5; of these drugs, piperacillin is least affected. The activity of clindamycin is similarly decreased. In addition, the accumulation of some drugs in white blood cells is impaired in an acidic environment. Changes in pH also lead to changes in the concentration of un-ionized and thus active drug. Weak bases such as aminoglycosides and fluorinated quinolones are predominantly ionized in an acidic environment and are less effective than in a less acidic environment, in part because of impaired diffusibility.

Low tissue oxygen tension, which can accompany pus, reduces white blood cell phagocytic and killing activity; slows the growth of organisms, making them less susceptible to many drugs; and specifically prevents the efficacy of aminoglyosides, which depend on active transport into bacterial organisms. The aerobic component (i.e., facultative aerobes) of a mixed infection may also be resistant to aminoglycoside therapy because the oxidative transport systems of such organisms (e.g., *E. coli*) may shut down in an anaerobic environment. β-Lactams are less effective in a hyperosmolar environment—which might occur as inflammatory debris accumulates—osmotic destruction of organisms is reduced.

The size of the bacterial inoculum can also influence antibiotic efficacy. The larger the bacterial inoculum at the target site, the greater the concentration (number of molecules) of antibiotic necessary to kill the organisms and the greater the risk of antibiotic destruction by enzymes produced by microorganisms. Host response to infection and its impact on antimicrobial therapy may vary with the organ system infected. For example, in respiratory tract infections, mucus produced by the host can directly interfere with antimicrobial therapy. Aminoglycoside efficacy may be decreased by chelation with magnesium and calcium in the mucus. Antibiotics may bind to glycoproteins, and mucus may present a barrier to passive diffusion. In addition, some antibiotics may alter the function of the mucociliary apparatus either by increasing mucous viscosity or by decreasing ciliary activity (e.g., tetracyclines).

Antimicrobials themselves can contribute detrimental factors to antibiotic efficacy. For example, the effect of selected antimicrobials on phagocytic function has been well established, although the clinical relevance of this effect is less clear (Labro, 1998).

Host Factors that Facilitate Drug Efficacy

Not all host factors negatively impact antimicrobial efficacy. For example, leukocytes at the site of inflammation may actively concentrate some antimicrobials (e.g., macrolides, lincosamides, and fluorinated quinolones) up to 20 to 100 or more times the PDC (Neu, 1994; Easmon and Crane, 1985; Tulkens, 1990; Hawkins et al., 1996). Thus, drugs that achieve only bacteriostatic concentrations in plasma may become bactericidal inside the cell, particularly against organisms that locate and survive inside cells (Fig. 8–14). Note, however, that drug accumulation does not

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Figure 8–13. Deposition of fibrous tissue in deep pyoderma presents a barrier to drug penetration.

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Figure 8–14. Intracellular organisms such as *Staphyloccocus* demonstrated in this special stain of infected skin may survive phagocytosis, serving to reinfect tissue once the phagocytic white blood cell has died.

necessarily enhance drug efficacy. Often the accumulated drug is sequestered into subcellular organelles where it cannot reach the organism. In addition, the drug may become otherwise inactivated once inside the cell. The different mechanisms of action of these drugs may not occur in an anaerobic environment, and concentrations by the white blood cells might be impaired in an anaerobic environment. The fluorinated quinolones are an example of a class of drugs whose uptake by WBCs is facilitated in an acidic environment; these drugs are distributed throughout the cytosol, where they remain active. The drug will leave the WBCs and enter a drug-free environment and thus may facilitate drug concentrations at the site of infection (Boothe, 1999). The effect of concentration by leukocytes on extracellular drug concentrations has yet to be established. On the one hand, local antibiotic concentrations may be reduced as the drug is sequestered by white blood cells, thus reducing the concentration of drug in the extracellular fluid. It is more likely, however, that drug concentrations will be increased as white blood cells die and release their intracellular contents.

IDENTIFYING DRUG FACTORS

Mechanisms of Drug Action

Knowledge of the mechanism of action target of a particular antimicrobial is important for several reasons.

1. The mechanism of action of a drug determines whether or not the antimicrobial can act in a bactericidal or bacteriostatic manner (assuming proper concentrations are achieved at the tissue site). Drugs that are capable of bactericidal effects at therapeutic doses are listed in Table 8–6. In general, drugs that target ribosomes such that bacterial growth is impaired (Fig. 8–15) tend to be static in action (the aminoglycosides are an exception). To be bactericidal, concentrations of these drugs will be toxic to the host.
2. The therapeutic efficacy of some antimicrobials can be impaired by host factors that alter the mechanism factor of the drug. Knowledge of the mechanism of action will facilitate anticipation of therapeutic failure. For example, β-lactams are less effective in a hypertonic environment such as might occur in the renal medullary interstitium or in the presence of inflammatory debris.
3. The mechanism of antimicrobial resistance often reflects the mechanism of resistance. Identifying mechanisms by which resistance might be avoided or minimized requires an appreciation of these mechanisms.
4. Understanding or anticipating host toxicity can be improved by understanding the mechanism of action of some antimicrobials.
5. A final need for understanding antimicrobial mechanisms of action is to provide a basis for the selection of antimicrobials to be used in combination. Such drugs should be selected based on mechanisms of action that complement rather than antagonize one another (see later discussion).

The cell wall is an important target for several antimicrobials, protecting the hypertonic intracellular environment of the organism from the hypotonic environment (Neu, 1994). A variety of proteins located in the cell wall (penicillin-bound proteins) are important in the formation of the cell wall during division of growth of the organisms. These proteins are the target of several antimicrobial agents. Destruction of the peptidoglycan layer, which provides support to the cell wall, increases the permeability of the cell wall to the hypotonic environment, resulting in osmotic lysis of the cell. Intracellular structures are also major targets for various antimicrobial agents. Binding of ribosomes, the site of protein synthesis in the cell, can either inhibit protein formation or result in the formation of faulty proteins that eventually prove detrimental to the organism. The nuclear material of microbes is another target: Interference with cellular DNA inhibits cellular division, as well as initial cellular functions. Generally, impaired DNA synthesis results in cell death. Other intracellular targets include selected metabolic pathways such as folic acid synthesis, which, when interfered with, prevents formation of materials vital to the microorganism.

Figure 8–15. Targets of antimicrobial actions.

Drug Disposition

Absorption

Care must be taken when selecting the antibiotic that the disposition of the drug meets the needs of the patient (see earlier discussion of host factors). The availability of drug preparations determines drug selection in many instances because not all drugs are available for administration by all routes. To maximize plasma and thus tissue drug concentrations, intravenous administration is the preferred route for critically ill patients or difficult to penetrate tissues; intramuscular and subcutaneous administration are the second and third choices, respectively. Oral absorption of antimicrobials, however, is preferred for long-term administration, for nonhospitalized patients, and when drug therapy is targeting the gastrointestinal tract.

Note that although a drug may be 100% bioavailable after oral administration (i.e., the drug is completed absorbed), the rate of absorption may be sufficiently slow that the peak effect is minimized (although the duration of drug in circulation may be prolonged). Efficacy may be impaired, particularly for organisms with a high MIC or for concentration-dependent drugs. Slow-release preparations, either orally or parenterally administered, should be used cautiously because prolonged absorption (controlled rate of release) may be so slow that therapeutic concentrations are not achieved. The risk of resistance is increased in such situations. Topical administration is the sole route for drugs that are too toxic to the host to administer systemically. Care must be taken, however, with drugs applied to skin whose surface has been damaged. Sufficient drug absorption may occur to render the patient at risk of developing toxicity. Drugs applied to the ear canal may be ototoxic, particularly in the presence of a perforated eardrum.

Distribution

Once in circulation, the antimicrobial must distribute well to target tissues (i.e., the site of infection). Anatomically, capillaries can be categorized to one of three types, each representing an increasing barrier to drug penetration (Ryan, 1993). Sinusoidal capillaries, found primarily in the adrenal cortex, pituitary gland, liver, and spleen, present essentially no barrier to drug movement. Fenestrated capillaries such as those located in kidneys and endocrine glands contain pores (50 to 80 nm in size) that facilitate movement between plasma and interstitium. Because the ratio of capillary surface area to interstitial fluid volume is so large, unbound drug movement from plasma into the interstitium occurs very rapidly in these tissues (Ryan, 1993: Barza, 1994). Continuous capillaries, such as those found in the brain, cerebrospinal fluid, testes, and prostate, present a barrier of endothelial cells with a tight junction (Ryan, 1993). For such tissues, this presents an additional barrier that is difficult to penetrate for drugs that are not lipid soluble. Muscle and adipose tissue also contain continuous capillaries.

Doses for drugs generally should be higher when treating infections in these tissues; particularly for water-soluble drugs. Comparison of MIC data with tissue drug concentrations may be useful when designing dosing regimens for such tissues.

Examples of different distribution patterns can be based on differences in volume of distribution (Vd) (Table 8–8; see also Table 8–4). Although the Vd of a drug does not indicate to which tissues drug is distributed, it can be used to approximate likelihood of tissue penetration. For example, water-soluble drugs tend to be distributed only to extracellular fluid and thus often have a Vd that approximates extracellular fluid (i.e., 0.2 to 0.3 L/kg). In contrast, a lipid-soluble drug can penetrate all membranes more easily and is thus more likely to be distributed to total body water; Vd will often approximate or exceed 0.6 L/kg. Drugs with a Vd greater than 0.6 L/kg may be accumulated in tissues (see Table 8–8). Urine and the central nervous system (CNS) offer two divergent examples of tissue penetration. Urine is easy to target by drugs renally eliminated. Other components of the urinary tract such as the kidney and, in particular, the prostate can, however, be more difficult to penetrate. Antimicrobial therapy of the

Table 8–8. Tissue Distribution Pattern of Selected Drugs

- Drugs distributed to extracellular fluid
  - β-Lactams
  - Aminoglycosides
- Drugs distributed to total body water
  - Chloramphenicol
  - Clindamycin
  - Doxycycline/minocycline
  - Erythromycin
  - Fluorinated quinolones
  - Sulfonamides/trimethoprim
- Drugs concentrated in urine
  - β-Lactams
  - Aminoglycosides
  - Fluorinated quinolones
  - Sulfonamides/potentiated sulfonamides
  - Vancomycin
- Drugs concentrated in bile
  - Clindamycin
  - Doxycycline/minocycline
  - Macrolides (erythromycin)
  - Rifampin
- Drug penetration of the blood-brain barrier
  - Readily enter the CSF
    - Chloramphenicol
    - Doxycycline/minocycline (unbound)
    - Fluorinated quinolones (for some organisms)
    - Metronidazole
    - Rifampin
    - Sulfonamides/trimethoprim
  - Enter the CSF in the presence of inflammation
    - Penicillins
    - Selected cephalosporins (e.g., cefotaxime, ceftriaxone, ceftazidime)
    - Fluorinated quinolones
    - Vancomycin
  - Do not enter the CSF
    - Aminoglycosides
    - Carbenicillin
    - Cephalothin
    - Cefazolin
    - Cefotetan
    - Clindamycin
    - Erythromycin
    - Tetracycline
- Drugs that accumulate in white blood cells
  - Clindamycin
  - Erythromycin (macrolides)
  - Fluorinated quinolones
  - Rifampin

Abbreviations: CSF = cerebrospinal fluid.

CNS is very difficult, although success may be facilitated by inflammation, which enhances drug penetration. However, once inflammation resolves, drug distribution may again decrease.

Lipid-soluble antimicrobials should be used for infections that are more difficult to treat, including those associated with tissue reaction or those caused by intracellular organisms, and when the site of infection presents a distribution barrier. Tissue distribution of aminoglycosides and most β-lactam antimicrobials is limited to extracellular fluid; in contrast, many other antibiotics (e.g., fluorinated quinolones, macrolides, and trimethoprim/sulfonamide combinations) are distributed well to all body tissues, including the prostate gland and eye. The blood-brain or CSF barrier represents a particularly challenging site because it not only prevents movement of antimicrobials into the CNS but also actively transports out or destroys some antimicrobials (i.e., selected cephalosporins) (see Table 8–8).

Imipenem, trimethoprim/sulfonamide, and fluorinated quinolones can achieve bactericidal concentrations for some infections in the CNS (particularly organisms with a low MIC); chloramphenicol will achieve bacteriostatic concentrations (LeFrock et al., 1984). Accumulation of antimicrobials in white blood cells facilitates treatment of intracellular infections (Easmon and Crane, 1985; Tulkens, 1990). Antimicrobials that are highly protein bound (e.g., doxycycline) may be less rapidly effective because only unbound drugs are pharmacologically active and drug distribution of unbound drug into the target tissue may take longer (Bergan, 1981; Craig and Ebert, 1989). Bound drugs do not distribute into tissues; furthermore, once at the site of infection, the drug can become bound once again to inflammatory proteins.

Drug movement into bacteria must also be considered (see Figs. 8–3 and 8–4). Gram-negative organisms offer a challenge different from that of gram-positive organisms. The efficacy of all antimicrobials depends on the drug reaching and penetrating the cell wall of the target organism. Although the cell wall of gram-positive organisms is often relatively accessible to chemotherapeutic agents, that of gram-negative organisms is protected beneath several layers of cell wall–associated structures. Proteins imbedded in the outermost membrane—known as *porins* or *outer membrane proteins*—form pores through which small molecules (including drugs) can penetrate (see Fig. 8–4). Although lipid-soluble drugs may be able to passively diffuse (to some degree) through this outer covering as well as through porins, for water-soluble drugs (e.g., β-lactams and aminoglycosides) the porins are the predominant method by which drugs are able to access the cell wall and thus subsequent movement into the organism (Neu, 1994). The size of porins varies between organisms, contributing to the differences in drug resistance that often characterize these microorganisms. For example, *Pseudomonas* species have very small porins, which exclude the penetration of many drugs. The efficacy of the extended penicillins (i.e., ticarcillin, piperacillin) results, in part, because of their smaller molecular weight and thus ease of penetration. Other proteins in the outside layer of gram-negative organisms act as active transport mechanisms, which may transport small molecules, including drugs, into the cell. Organisms can change the lipid or cationic component of the LPS, thus impeding drug penetrability.

The roles of drug pK_a and the environmental pH of a target tissue on drug efficacy have already been addressed. Ionization may impair drug movement through the LPS for drugs that passively move through this layer.

Drug Elimination

The route through which the drug is eliminated is an important consideration for two reasons. First, if the target tissue is also a route of elimination for that drug, higher drug concentrations can be expected at the site. Second, if the drug is toxic to an organ of elimination, use of the drug should be avoided if the organ is already diseased. Finally, if the drug is toxic to any tissue, the drug should be used cautiously in the presence of disease in the organ of elimination, or dosing regimens should be appropriately modified.

Resistance to Antimicrobials

Mechanisms of Transmission

The role of resistance in therapeutic failure of antimicrobials is well established (Neu, 1994; Tomasz, 1994). The ability of organisms to develop resistance to an antimicrobial varies with the species and strain. Resistance might be inherent or acquired. Inherent resistance is exemplified by the lack of efficacy of aminoglycosides against anaerobic organisms because the drugs must be actively transported into the cell (oxygen dependent). Acquired resistance can occur during the course of therapy (leading to changes in a culture and susceptibility pattern).

Acquired resistance can reflect a mutational change (e.g., a chance mutation in the genetic material or the transfer of genetic material between organisms), most commonly, but not exclusively, in a plasmid. Mutational resistance occurs slowly and often is accompanied by other changes that render the organism less viable and thus more likely to be destroyed by other drugs. Transduction (especially by staphylococcal organisms; material is copied by a phage) and transformation are less common methods by which organisms can acquire extrachromosomal DNA. In contrast to mutational resistance, plasmid-mediated resistance, particularly that transmitted by conjugation, is a clinically relevant method of transfer that impacts therapeutic success. Plasmid-mediated resistance in gram-negative organisms is common, can develop rapidly, and can be transmitted between species (among gram-negative and between gram-negative and gram-positive organisms). A single transfer of plasmid genetic material from a bacterial donor can result in antimicrobial resistance against up to seven antimicrobials in the recipient bacterial cell during therapy.

Biochemical Mechanisms of Resistance

The mechanisms of bacterial resistance vary and involve changes in porin sizes for gram-negative organisms (most drugs), cell wall structures, proteins (e.g., penicillin-binding proteins), or enzymes; development of enzymes that destroy antimicrobials (e.g., aminoglycosides, β-lactamases that destroy penicillins [see Fig. 8–3]), alkyltransferases that destroy chloramphenicol, development of efflox proteins that pump drug out of the organism (e.g., fluorinated quinolones and tetracyclines); or changes in metabolic pathways (sulfonamides) or binding sites (i.e., on ribosomes as for aminoglycosides for antibiotics) (Zhao et al., 1997; Cohen et al., 1989). Organisms are likely to have more than one mechanism of resistance. Indelible resistance is well documented for some organisms against selected β-lactamases and has been described against fluorinated quinolones and others. Bacteria often respond to the presence of the antimicrobial by altering their physiology such that resistance occurs. One of the reasons that *Pseudomonas* species are so difficult to treat is their ability to alter porin size in response to the presence of an antimicrobial. Smaller porin sizes preclude drug movement through the LPS capsule. β-Lactamase formation is inducible in *Staphylococcus* species; formation greatly increases in the presence of a β-lactam antibiotic.

Avoiding Antimicrobial Resistance

Actions should be taken to avoid antimicrobial resistance not only for the patient but also for the medical community. Even if an antimicrobial is characterized by a low to nonexistent incidence of plasmid-mediated resistance (such as the fluorinated quinolone antibiotics), resistance to drugs takes several decades to develop. Thus, actions should be taken proactively such that the likelihood of resistance developing against a group of antimicrobials is reduced.

The recent use of antimicrobials for the patient should be considered when selecting an antimicrobial (Neu, 1994). The development of infection despite recent or ongoing antimicrobial therapy suggests that the infecting organism is resistant to the antibiotic chosen or an inappropriate dosing regimen is being used. Basing drug selection on culture and susceptibility information is probably the best method to reduce the risk of resistance. Secondary resistance can also occur during the course of antimicrobial therapy, however, even if selection is based on culture and susceptibility data. Pharmaceutical manufacturers have been able to manipulate antimicrobial drugs in a variety of ways such that resistance is minimized and these options can be selected in an attempt to minimize resistance. For example, bacterial resistance has been decreased by synthesizing smaller molecules that can penetrate smaller porins (e.g., the extended spectrum penicillins ticarcillin and piperacillin); "protecting" the antibiotic (e.g., with clavulanic acid, which "draws" the attention of the β-lactamase away from the penicillin); modifying the compound so that it is more difficult to destroy (e.g., amikacin, which is a larger and more difficult to reach molecule than gentamicin); and developing lipid-soluble compounds that are more able to achieve effective concentrations at the site of infection (e.g., doxycycline compared with other tetracyclines).

Probably the single most important action that can be taken to reduce the incidence of resistance is to ensure that adequate drug concentrations are reached at the site of infection. The development of resistance in critical or chronic situations can be minimized by ensuring that organisms are exposed to maximum drug concentrations for a sufficient period of time. Thus intravenous administration should be considered in selected situations such as life-threatening conditions or prophylactic therapy or for difficult to penetrate tissues; doses should be maximized and based on MIC and therapeutic drug monitoring whenever possible; and the proper dosing interval should be used for time-dependent antibiotics. Host factors should be considered in the design of the dosing regimen. Drugs inherently more resistant to bacterial inactivation should be selected (e.g., amikacin rather than gentamicin). Combination antimicrobial therapy (such as β-lactamase–protected antimicrobial combinations; combination of β-lactams with aminoglycosides) also reduces the incidence of resistance.

Drug Toxicity

Because host cells are eukaryotic and the targets of most antimicrobials are prokaryotic bacterial cells, the toxicity of antimicrobials frequently is not related to the mechanism of antimicrobial action. Rather, toxicities tend to be of an allergic basis or due to mechanisms unrelated to drug mechanism of action. For example, β-lactam antibiotics are generally considered very safe and should be because their efficacy depends on the bacterial cell wall—a cellular structure missing in mammalian cells. Often, even if cellular structures are present in both microbe and host, slight differences in the structure will result in different antimicrobial binding properties. For example, sulfonamides and fluorinated quinolones tend to be safe because the antibiotics have a much greater affinity for the bacterial target enzymes than the mammalian enzymes. For selected antimicrobials, however, the mechanism of toxicity can be related to the mechanism of drug action, particularly if the microbe target is similar in structure to the host target. For example, colistin and polymyxin both target the cell membrane, which is similar enough between bacterial and mammalian cells to cause toxicity. Some drugs that inhibit protein synthesis by binding to ribosomes (e.g., tetracyclines and chloramphenicol) will cause antianabolic effects in the host at sufficiently high doses. For some drugs, host toxicity may occur through mechanisms unrelated to its mechanism of action yet as a result of targeting structures in host cells. For example, aminoglycoside toxicity occurs because the drugs are actively accumulated in renal tubular cells in the same manner that they are accumulated in bacterial organisms.

A less common cause of therapeutic failure as a result of host factors is drug-induced allergy. Some drugs directly cause mast cell degranulation; occasional anaphylactoid reactions to some intravenously administered antibiotics may reflect this reaction, which should not be considered a true "allergy" because it can occur with the first dose. The fluorinated quinolones are associated with histamine release, and rapid intravenous administration should be avoided. Anaphylactoid reactions can be minimized by administration of a small first dose before therapy. In contrast, drug-induced allergies generally require previous administration or a duration of therapy sufficient to allow antibody formation to the drug, which acts as a hapten (generally 10 to 14 days). Few drug allergies have been documented in animals. Among the most notorious are reactions to the potentiated sulfonamides. Reactions to β-lactams, tetracyclines, and other drugs cause miscellaneous reactions (see discussions of individual drugs in Chapter 9).

Actions that minimize host toxicity enhance therapeutic success. The role of proper dose calculation, therapeutic drug monitoring, and combined antimicrobial therapy are addressed later in the context of enhancing therapeutic efficacy. Care must be taken that targeted peak PDCs are not close to toxic concentrations. For most antimicrobials, the incidence of predictable (type A) drug reactions correlates with maximum or peak PDC. For aminoglycoside-induced nephrotoxicity and ototoxicity, however, the minimum or trough PDCs determine toxicity (Bennett et al., 1979; Maller et al., 1991; Reiner et al., 1978). Specific actions to minimize toxicity of aminoglycosides and other antimicrobials are addressed elsewhere with each antibiotic. The use of topical or local antimicrobial therapy in the skin, eye, ear, and urinary, gastrointestinal, and respiratory systems can also be implemented if the antimicrobial is not absorbed from the site of topical administration (e.g., aminoglycosides). However, note the potential ototoxicity of many topically applied drugs. For lipid-soluble drugs or for water-soluble drugs applied to damaged skin, however, lack of absorption from topical sites should not be assumed. The roles of subtherapeutic drug concentrations in tissues other than the site of topical drug administration and the development of resistant microorganisms have not yet been elucidated.

Release of endotoxin may influence antimicrobial selection for the patient infected with a large number of gram-negative organisms (Nitsche et al., 1996). Endotoxins cause further release of cytokines and other mediators of septic shock (see Chapter 10). Most of these effects are mediated by the inner lipid A component of the LPS molecule that becomes exposed after antimicrobial therapy. In human patients suffering from endotoxic shock, outcome of antimicrobial therapy has been related to plasma endotoxin levels. A number of antibiotics cause release of endotoxin from gram-negative organisms. Attempts have been made to correlate the amount of endotoxin released to the class of antimicrobial and specifically to its mechanism of action.

Continued bacterial growth or rapid cell lysis and death have been suggested to be important criteria for endotoxin release after antimicrobial therapy. In contrast, the rate of bacterial killing and antimicrobial efficacy do not appear to be related to the rate and amount of endotoxin release. Among the drugs traditionally used to treat septicemia, aminoglycosides have been associated with the least endotoxin release and β-lactams with the greatest release (with imipenem being a notable exception). Reported amounts of quinolone release vary. The magnitude of endotoxin release can vary with the specific drug within an antimicrobial class. For example, in a study of mouse *E. coli* peritonitis, imipenem and ciprofloxacin caused less endotoxin release than did cefotaxime (Nitsche et al., 1996). In fact, imipenem stands out among the β-lactams in causing the least amount of endotoxin release.

The different amounts of endotoxin released by β-lactams may reflect different affinities of the drugs for different penicillin-binding proteins of the organism. The release of endotoxin may also be dose (concentration) dependent. For example, endotoxin release is greater at half the recommended dose of ciprofloxacin (3 mg/kg vs. 7 mg/kg ciprofloxacin) according to the previously described model (Nitsche et al., 1996). Actions that might minimize the sequelae of endotoxin release after antimicrobial therapy have not been established. Presumably, administering a dose more slowly may decrease the rate of endotoxin release. Binding and subsequent inactivation of endotoxin by antimicrobials has been documented, particularly for cationic antimicrobials such as the quinolones, aminoglycosides, and polymyxin (Nitsche et al., 1996; Aoki et al., 1994). The clinical relevance of endotoxin binding by antimicrobials has yet to be established.

ENHANCING ANTIMICROBIAL EFFICACY

Proper Dose and Route

Antimicrobial therapy must be implemented in a timely fashion. A dose of antimicrobials administered at the first appearance of a clinical infection has a much greater therapeutic effect than therapy initiated a week later. Although labeled dosing recommendations generally should be followed, exceptions occur as we learn more about optimizing antimicrobial therapy. In general, to maximize efficacy, doses should be increased particularly for serious or chronic infections, tissues that are difficult to penetrate, or infections associated with detrimental changes at the site of infection. Product labels may not reflect new findings regarding antimicrobial efficacy because pharmaceutical companies may choose not to endure the costs associated with gaining approval for a new label that reflects the new dosing regimen. Dose modification beyond that on the label should be based on current literature. Therapeutic drug monitoring can be used to establish a dose or interval for a drug for the individual patient and is ideally the basis of dose modification for critical patients. Unfortunately, few drugs can be rapidly and accurately measured at a reasonable cost (primarily the aminoglycosides).

Alternatively, with sufficient knowledge of the antimicrobial, the dose can be calculated from MIC data (see Tables 8–4 and 8–5) (Brown, 1987; Schentag, 1991; Carbon, 1992). The dose of an antibiotic depends on a target concentration (i.e., the MIC times the therapeutic factor) and the drug Vd as reported in the literature (see Table 8–4) and modified for the patient if indicated (e.g., for dehydration or intensive fluid therapy). For example, using a target for amikacin of 4 μg/mL (see Fig. 8–8) and the reported Vd in Table 8–4 (0.23 L/kg), a dose for amikacin can be calculated for a patient infected with this *E. coli* (see Fig. 8–10). The maximum therapeutic factor that can be used while not surpassing the breakpoint for amikacin is 8 (32 μg/mL ÷ 4 μg/mL = 8). The dose of amikacin then would be 4 μg/mL (mg/L) • 8 • 0.23 L/kg or 7.3 mg/kg, which is within the recommended dose. Note that larger therapeutic factors could probably be used in this instance because drug concentrations that surpass the current breakpoint of the various aminoglycosides have been surpassed with no apparent increase in toxicity as long as recommended trough concentrations are achieved during the dosing interval. Thus a therapeutic factor of 10 would not be unreasonable even though the published breakpoint would be surpassed (4 μg/mL • 10 • 0.23 L/kg = 9.2 mg/kg). In fact, much higher doses of amikacin are currently recommended for once daily therapy.

For enrofloxacin, since the reported breakpoint is only twofold different from the MIC, the maximum therapeutic factor that theoretically could be used while remaining below the breakpoint is 2. The dose would be 1 μg/mL • 2 • 2.6 L/kg or 5.2 mg/kg. The therapeutic factor is small in this case, and effective concentrations may not be achieved for some tissues. If a more reasonable therapeutic factor were used (to achieve a high inhibitory quotient), such as 8, the dose would have to be 20 mg/kg, which now is within the labeled dose (5 to 20 mg/kg once daily [Boothe, 2000a]). Note that changes in the Vd in animals must be taken into account when doses are calculated.

Drugs may be selected based on their route of administration. Not all drugs are available for parenteral or oral administration. Parenteral and particularly intravenous, administration is indicated for life-threatening infections or any time tissue concentrations need to be maximized. Parenteral drugs are also indicated for the vomiting animal. Oral drugs are indicated for long-term use, outpatient therapy, and treatment of gastrointestinal tract illness. Topical therapy may be selected to enhance drug delivery while minimizing toxicity. Topical therapy with lipid-soluble drugs might, however, best be limited to situations in which systemic therapy of the same drug is implemented, thus avoiding development of subtherapeutic drug concentrations in tissues other than the site of topical application, as might occur if topical administration alone is implemented.

Combination Antimicrobial Therapy

Combination therapy can be used to achieve a broad antimicrobial spectrum for empirical therapy, treat a polymicrobial infection involving organisms not susceptible to the same drugs, reduce the likelihood of antimicrobial resistance, and reduce the risk of adverse drug reactions by minimizing doses of potentially toxic antimicrobials (Schimpff et al., 1989; Kapusnik et al., 1989; Neu, 1994; Boothe, 2000c). Rational combination antimicrobial therapy may be the single most effective action taken to enhance antimicrobial efficacy for the chronic or serious infection. The primary reasons to avoid combination therapy include increases in the risks of suprainfection and of toxicity (if both drugs are potentially toxic), high cost, and inconvenience to the patient (Kapusnik et al., 1989).

Synergism and Antagonism

Antimicrobials to be used in combination therapy should be selected rationally and should be based on target organisms as well as on mechanism of action. Combinations might result in antagonistic, additive or synergistic antimicrobial effects (Fig. 8–16 and Table 8–9) (Eliopoulos and Moellering, 1996). Generally, these effects are defined in in vitro systems; clinical relevancy is more difficult to establish. Also, the combined effects of two or more antimicrobials is likely to differ with the organism. Avoidance of *antagonism* is particularly important to patients with inadequate host defenses (Schimpff et al., 1989; Kapusnik et al., 1989; Neu, 1994; Eliopoulos and Moellering, 1996). In general, "bacteriostatic" drugs that inhibit ribosomes and thus microbial growth (e.g., chloramphenicol, tetracyclines, and erythromycin) should not be combined with drugs whose mechanism of action depends on protein synthesis such as growth of the organism (e.g., β-lactams) or formation of a target protein. The bactericidal activity and continued degradation or destruction of the microbial target β-lactams and fluorinated quinolones depend on continued synthesis of bacterial proteins. Antagonistic effects have been well documented between β-lactam antimicrobials and inhibitors of ribosomal activity. The degree of antagonism between fluorinated quinolones and growth inhibitors is controversial; antagonism has been reported with the use of ciprofloxacin and chloramphenicol (Eliopolous and Moellering, 1996), but impaired efficacy was not detected in other studies (Zeiler and Voight, 1987). Antagonism between chloramphenicol and gentamicin has also been documented (Eliopolous and Moellering, 1996).

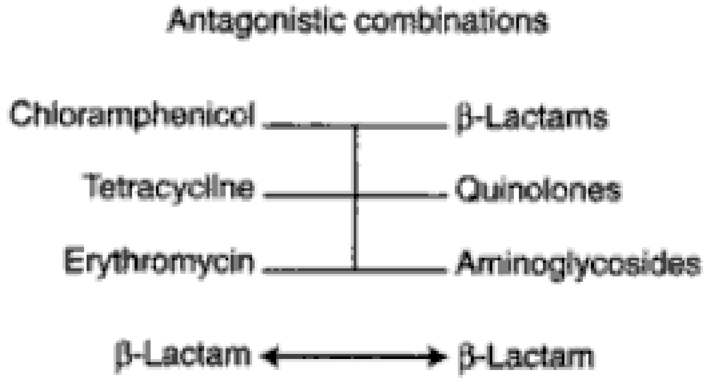

Figure 8–16. Combinations of antimicrobials can have different sequelae. Antagonistic antimicrobial combinations are perhaps best exemplified when a drug that inhibits bacterial growth is combined with a drug whose action depends on rapid cell growth.

Chemical antagonism is also possible between two or more antimicrobials (Zeiler and Voight, 1987; King, 1989) (see Chapter 2). Aminoglycosides and quinolones are chemically inactivated by penicillins at sufficient concentrations. Ticarcillin has been used therapeutically to reduce the risk of toxicity in a patient overdosed with an aminoglycoside (Olin, 1992). Chemical antagonism is unlikely in most clinical uses of these drugs. The risk of antagonism is increased, however, with simultaneous intravenous use of high doses of both ticarcillin and aminoglycosides such as might occur if aminoglycosides are administered once daily. Potential chemical interactions between other antimicrobials should be identified before combination therapy. Certainly, antimicrobials should not be mixed in the same syringe or intravenous line unless a lack of antagonism has been confirmed (King, 1989).

Drugs that have the same mechanism of action would act in an additive fashion. For example, chloramphenicol and clindamycin bind the same 50S ribosomal subunit and will antagonize one another, but, because tetracyclines bind to the 30S subunit, the combination of either drug with a tetracycline conceivably might be additive (although this has not been studied). Additive effects probably occur when active metabolites are produced from an active parent compound, such as metabolism of enrofloxacin to

Table 8–9. Examples of Synergistic Drug Combinations

Drug One	Drug Two	Organisms
Dicloxacillin	Ampicillin, penicillin, cephalothins	*Escherichia coli, Klebsiella, Pseudomonas aeruginosa*
β-Lactam: cephalothin, ampicillin, piperacillin, cefotaxime, cefamandole	Aminoglycoside: gentamicin, amikacin	*Escherichia coli, Pseudomonas aeruginosa*, enterococci, others
Chloramphenicol	Ampicillin	*Salmonella typhimurium, Staphylococcus aureus* (effect is bacteriostatic in nature)
Penicillin	Gentamicin	*Bacteroides melaninogenicus*
Imipenem	Vancomycin	*Staphylococcus aureus*
β-Lactam, vancomycin	Aminoglycoside	*Staphylococcus aureus*
Trimethoprim/sulfonamide	Imipenem, amikacin	*Nocardia asteroides* (effect is bacteriostatic)
Imipenem	Trimethoprim/sulfonamide, cefotaxime	*Nocardia asteroides* (effect is bacteriostatic)
Ethambutol	Rifampin, aminoglycosides, ciprofloxacin (enrofloxacin), clarithromycin	*Mycobacterium avium* (effect is bacteriostatic)

From Wiedemann B, Atkinson BA: Susceptibility to antibiotics: species incidence and trends. In Lorian V (ed): Antibiotics in Laboratory Medicine, pp 900–1168. Baltimore, Williams & Wilkins, 1996.

ciprofloxacin (Kung et al., 1993). Antagonistic effects might occur, however, if the drugs compete for a limited number of target sites (e.g., chloramphenicol and erythromycin). In contrast, synergistic actions might occur if the antimicrobial targets are subtly different. For example, a combination of different β-lactams generally results in additive antimicrobial activity. If the two microbials target different penicillin-binding-proteins, however, their combined effect may actually be synergistic ("double β-lactam therapy") (Hopefl, 1991; Pedler and Bint, 1984). In contrast, combinations of other β-lactam antibiotics (including combined selected cephalosporins) are antagonistic (Pedler and Bint, 1984). The different sequelae of combined β-lactam therapy might be caused by the penicillin-binding proteins targeted by each drug.

Synergism between antimicrobials can occur if the two antimicrobials kill bacteria through independent mechanisms or through sequential pathways toward the same target (Richards and Xing, 1993; Eliopoulos and Moellering, 1996). The combination of trimethoprim and a sulfonamide exemplifies synergism resulting from sequential actions in the same metabolic pathway (see discussion of potentiated sulfonamides). Clavulanic acid "draws" the β-lactamase activity of the microorganism away, allowing the protective β-lactam to do its job. Synergism between β-lactams and aminoglycosides exemplifies synergism due to killing by independent pathways. Synergism is expected because their mechanisms of action complement one another, but efficacy is enhanced further because aminoglycoside movement into the bacteria is enhanced by increased cell wall permeability induced by the β-lactam (Eliopoulos and Moellering, 1996). Enhanced movement in a bacteria may occur with other drugs (e.g., potentiated sulfonamides) when combined with β-lactams.

Polymicrobial Infections

Combination antimicrobial therapy may be selected because of the presence of a polymicrobial infection (Fig. 8–17) (Kapusnik et al., 1989; Neu, 1994; Boothe, 1990;

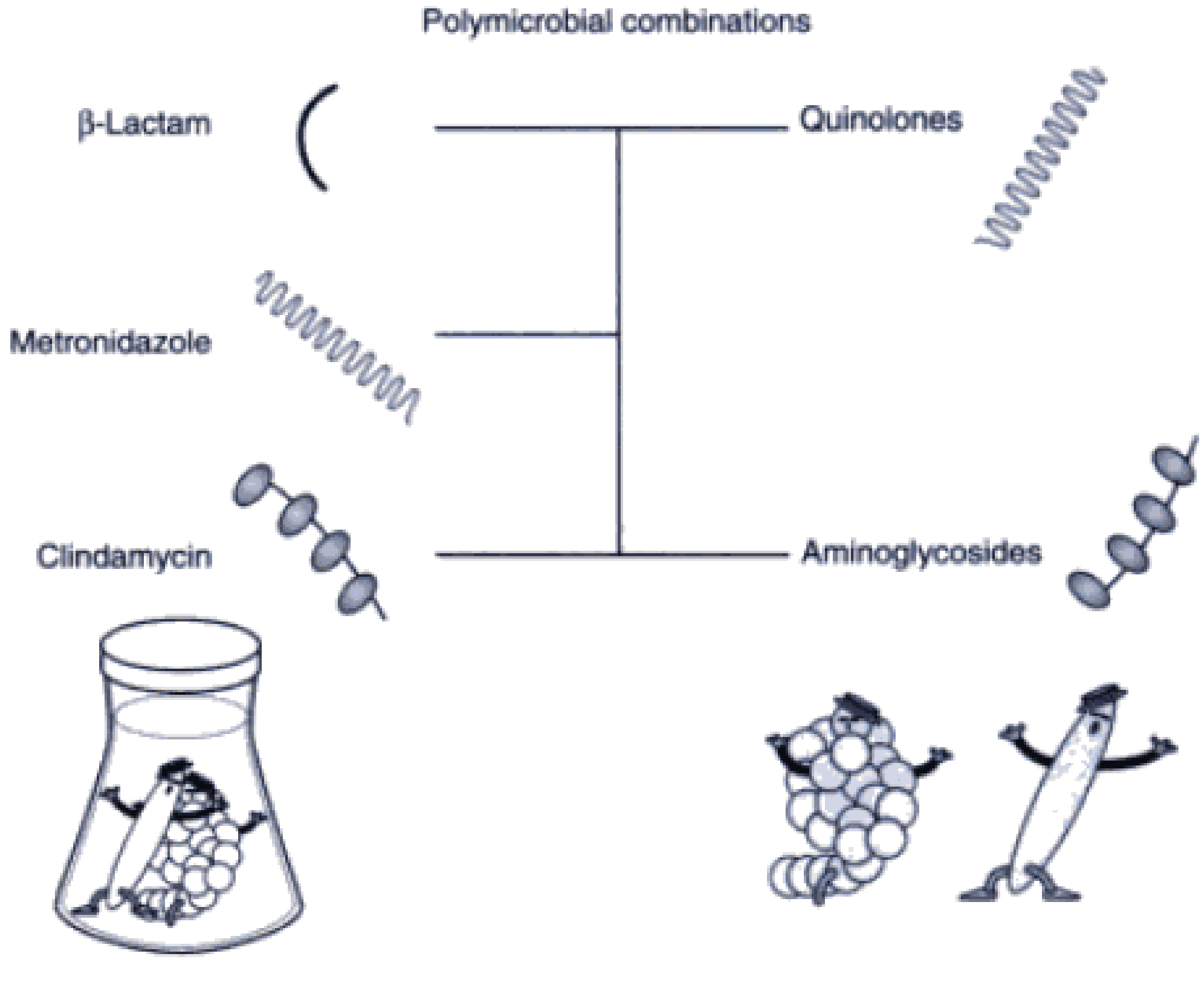

Figure 8–17. Polymicrobial infections may require combination therapy. The quinolones and aminoglycosides offer excellent aerobic gram-negative coverage; the β-lactams (especially penicillins), metronidazole, and clindamycin offer excellent gram-positive and anaerobic coverage.

Nostrandt, 1990). Aminoglycosides or fluorinated quinolones are often combined with β-lactams, metronidazole, or clindamycin in order to target both aerobic gram-positive and gram-negative infections or aerobic infections caused by both aerobes and anaerobes. The combined use of selected antibiotics may result in therapy effective against a given microbe when either drug alone was ineffective.

MISCELLANEOUS CONSIDERATIONS

Convenience and Cost

Convenience of administration for outpatient therapy may profoundly alter drug efficacy simply because of owner compliance. The cost of antimicrobials certainly impacts antibiotic selection but should only be a factor after other considerations have been taken into account. The cost of an excellent antimicrobial can be easily surpassed by the selection and use of several less expensive, yet less effective antimicrobials.

Evaluating Response to Therapy

Evidence of improvement in clinical status or decline should occur within 48 to 72 hours of starting antimicrobial therapy (Kapusnik et al., 1989). Although fever and leukocytosis have been the hallmark indicators of the need for antimicrobial therapy, there are other causes of inflammation and fever besides infection. In addition, leukocytosis may be absent in the immunocompromised patient. Therapeutic failure may reflect an inappropriate antimicrobial selection, an improper dose or interval, or a number of host factors as previously discussed. Therapeutic drug monitoring can (although care must be taken not to assume that PDC equals tissue concentrations), help discern between the first two causes of therapeutic failure as can repetitive culture and susceptibility testing. Timing of repeated susceptibility testing is controversial. Ideally, another culture several days or 1 to 2 weeks into therapy (depending on duration of therapy) and again at the same time after therapy has been discontinued will document success or failure.

When antimicrobials are changed because of therapeutic failure, the least expensive and least toxic antimicrobial that shows efficacy on culture should be chosen. Note, however, that factors altering drug efficacy or movement to the target site must also be considered. The antimicrobial with the narrowest spectrum also should be used to minimize suppression of normal flora and the risk of antimicrobial resistance (Kapusnik et al., 1989; Schimpff et al., 1989). Equivocable response to antimicrobial therapy may indicate the need to add another antimicrobial in order to cover potentially resistant organisms. Duration of therapy should be sufficiently long to allow complete resolution of infection, yet short enough to avoid toxicity, development of resistance, and suprainfection. Duration of antimicrobial therapy should vary with the severity of illness; 10 to 14 days is generally recommended for granulocytopenic, septicemic, and seriously ill patients, whereas 7 to 10 days of therapy may be sufficient for patients with less severe infections. Febrile patients should be treated until they have been afebrile for 4 to 5 days (Kapusnik et al., 1989; Schimpff et al., 1989). Chronic infections may require 6 to 8 weeks or more of therapy.

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9 Antimicrobial Drugs

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INTRODUCTION
β-LACTAM ANTIBIOTICS
- Mechanism of Action
- Spectrum of Activity
- Resistance
- Pharmacokinetics
- Adverse Effects
- Therapeutic Use

AMINOGLYCOSIDES
- Mechanism of Action
- Spectrum of Activity
- Resistance
- Pharmacokinetics
- Adverse Effects
- Therapeutic Use

FLUORINATED QUINOLONES
- Structure-Activity Relationship
- Mechanism of Action
- Spectrum of Activity
- Resistance
- Pharmacokinetics
- Drug Interactions
- Adverse Reactions
- Therapeutic Use

TRIMETHOPRIM OR ORMETOPRIM/SULFONAMIDE COMBINATIONS: INHIBITORS OF FOLIC ACID SYNTHESIS
- Mechanism of Action
- Spectrum of Activity
- Resistance
- Pharmacokinetics
- Adverse Effects
- Therapeutic Use

TETRACYCLINES AND CHLORAMPHENICOL
- Mechanism of Action
- Spectrum of Activity
- Resistance
- Pharmacokinetics
- Adverse Effects

LINCOSAMIDES: LINCOMYCIN AND CLINDAMYCIN
MACROLIDES
VANCOMYCIN
RIFAMPIN
MISCELLANEOUS ANTIBIOTICS
- Bacitracin
- Novobiocin
- Polymyxins
- Nitrofurans
- Methenamine
- Metronidazole

INTRODUCTION

The principles that guide proper antimicrobial selection are discussed in Chapter 8. This chapter focuses on the individual drugs by describing their characteristics and how they impact therapeutic success. Characteristics discussed for each drug class include the mechanism of antimicrobial action (Table 9–1), the disposition of the drugs in the patient (see Table 8–4), the spectrum of antimicrobial action of each drug (Table 9–2), and adverse effects. Antimicrobial drugs are most often categorized based on mechanism of action (Fig. 9–1; see Table 9–1). This categorization based on mechanism of drug action is followed in this chapter because it is pertinent to therapeutic success for several reasons. The mechanism of action of each drug determines drug efficacy (i.e., bactericidal vs. bacteriostatic), safety (to some degree), and the mechanisms of resistance. Mechanism of action is also important to the selection of combination antibiotic therapy. With the exception of drugs that are approved only for use in animals, much of the information regarding antimicrobial use in veterinary patients is extrapolated from use in human patients.

β-LACTAM ANTIBIOTICS

The broad spectrum, low toxicity, and reasonable cost of β-lactam antibiotics results in their frequent use for treatment of infections. In addition, β-effects on cell wall synthesis result in their frequent selection for combination antimicrobial therapy. The β-lactam antibiotics include the cephalosporins, the combination penicillin/β-lactamase inhibitors, and carbepenems (see Table 9–1).

Mechanism of Action

β-Lactam antibiotics contain a four-member β-lactam ring that is the active site of the drug and a second member ring whose structure differs between cephalosporins (seven member) and penicillins (six member) (Fig. 9–2) (Neu, 1994; Kapusnik et al., 1989; Bush et al., 1989; Donowitz, 1989; Vaden and Riviere, 1995). The mechanism of action of β-lactams, regardless of the type, is interference with bacterial cell wall synthesis (Fig. 9–3). The bacterial cell wall is comprised of several layers of a peptidoglycan matrix. Rigidity of the cell wall is accomplished through cross-binding of the peptidoglycan strands in the matrix. The peptidoglycan strands are composed of five repeating disaccharide units of *N*-acetylglucosamine and *N*-acetylmuramate; these units are formed by the bacteria in stages. A pentapeptide, which ends with an D-Ala-D-Ala terminus, is attached to each of the repeating units of these disaccharides. The units are joined to form a chain or peptidoglycan strand. The resulting chains are then cross-linked to provide cell wall rigidity.

Cross-linking between the D-Ala-D-Ala terminals is catalyzed by a transpeptidase enzyme, one of several penicillin-binding proteins (PBPs) located in the cell wall (see Fig. 9–3). The bacterial substrate for the transpeptidase enzyme is the pentapeptide of the peptidoglycan and, specifically, the terminal amino acids D-Ala-D-Ala. The β-lactam ring of the β-lactam antibiotics is structurally simi-

Table 9–1. Drugs Listed by Class and Mechanism of Action

Class or Drug	Mechanism	Subclass	Category	Drug	Comments
ß-Lactam	Cell wall inhibitor	Penicillin	Natural	Penicillin G (procaine, benzathine, Na and K salts)	Various esters that prolong release
			Semisynthetic, ß-lactamase resistant	Dicloxacillin, oxacillin	
			Semisynthetic, aminopenicillin	Amoxicillin, ampicillin	Available with clavulanate
			Synthetic, extended spectrum	Piperacillin, ticarcillin, carbenicillin	Available with clavulanate
			Carbapenem	Imipenem	
		Cephalosporin	First generation	Cefadroxil, cefazolin, cephalothin, cephalexin, cephapirin, cephradine	Cephaloridine no longer manufactured
			Second generation	Cefamandole, cefoxitin, cefuroxime, cefaclor	
			Third generation	Cefotaxime, cefotetan, ceftazidime, ceftizoxime, ceftiofur, ceftriaxone	
Vancomycin	Cell wall inhibitor			Vancomycin	
Bacitracin	Cell wall inhibitor				
Aminoglycoside	Ribosomal inhibitor			Amikacin, gentamicin, kanamycin, tobramycin	
Quinolone	DNA gyrase inhibitor	Fluorinated		Enrofloxacin, ciprofloxacin, norfloxacin	
Sulfonamides	Folic acid inhibitor			Sulfadiazine, sulfamethoxazole, sulfadimethoxine (with trimethoprim or ormetoprim)	
Polymyxin	Cell membrane			Polymyxin; colistin is a related drug	
Tetracycline	Ribosomal inhibitor			Chlortetracycline, doxycycline, oxytetracycline, tetracycline	
Chloramphenicol	Ribosomal inhibitor			Chloramphenicol, florphenicol	Illegal in food animals
Macrolides	Ribosomal inhibitor			Erythromycin, azithromycin	
	Ribosomal inhibitor			Tilmicosin	
Lincosamides	Ribosomal inhibitor			Lincomycin	
	Ribosomal inhibitor			Tylosin	
	Ribosomal inhibitor			Clindamycin	
Rifampin	DNA polymerase				
Metronidazole	DNA			Metronidazole	

Table 9–2. Relative Spectrum of Activity of Selected Antimicrobials‡

Drug	Gram Positive	Gram Negative	*Pseudomonas*	Anaerobic	*Clostridium*	Other
Penicillin G	4+*	1+	—	4+	4+	—
Dicloxacillin	4+	—	—	—	—	—
Amoxicillin	4+*	2+	—	3+	3+	—
Amoxicillin/clavulanate	4+	2+	—	4+	3+	—
Ticarcillin	4+*	4+	4+	4+	4+	—
Imipenem	4+	4+	4+	4+	4+	—
Cefazolin	3–4+†	2–3+	—	—	1–2+	—
Cephalothin	3–4+†	2–3+	—	—	1–2+	—
Cefoxitin	2–3+	3+	—	3–4+	3+	—
Cefadroxil	2–3+	2–3+	—	1+	—	—
Cefotaxime	1+	3–4+	3–4+	1–2+	—	—
Ceftiofur	3+†	2–3+	—	2–3+	2–3+	—
Aminoglycosides	3+†	4+	4+	—	—	—§, ‖, ¶
Fluorinated quinolones	3+†	4+	4+	—	—	—§, ‖
Sulfonamide/trimethoprim/ ormetoprim	2–3+	2–3+	—	2–3+	2–3+	—‖, **
Tetracycline	2+	2+	—	2–3+	2–3+	—††, ‡‡
Doxycycline	2+	2+	—	2–3+	2–3+	—††, ‡‡
Chloramphenicol	2–3+	2–3+	—	2–3+	2–3+	—‡‡
Clindamycin	4+	—	—	4+	2–3+	—
Lincomycin	2–3+	—	—	+	+	—
Tylosin	2–3+	—	—	+	+	—
Erythromycin	2–3+	—	—	+	+	—
Rifampin	3+	+	—	—	—	—
Metronidazole	§§	§§	—	4+	4+	—
Vancomycin	5+	—	—		3–4+	—§

*ß-Lactamase sensitive.

†Particularly *Staphylococcus* species.

‡The spectra are relative only. The package insert of each drug, and, in particular, of the cephalosporins, should be reviewed prior to treatment in order to identify appropriate spectra.

§Effective against selected *Mycobacterium* species.

‖Effective against *Actinomyces* species.

¶Amikacin is effective against *Nocardia* species.

**Effective against *Nocardia* species.

††Effective against selected *Myocoplasma, Rickettsia,* and *Chlamydia* species.

‡‡Effective against *Hemobartonella* species.

§§|||Metronidazole is effective against anaerobic gram-positive and gram-negative organisms only.

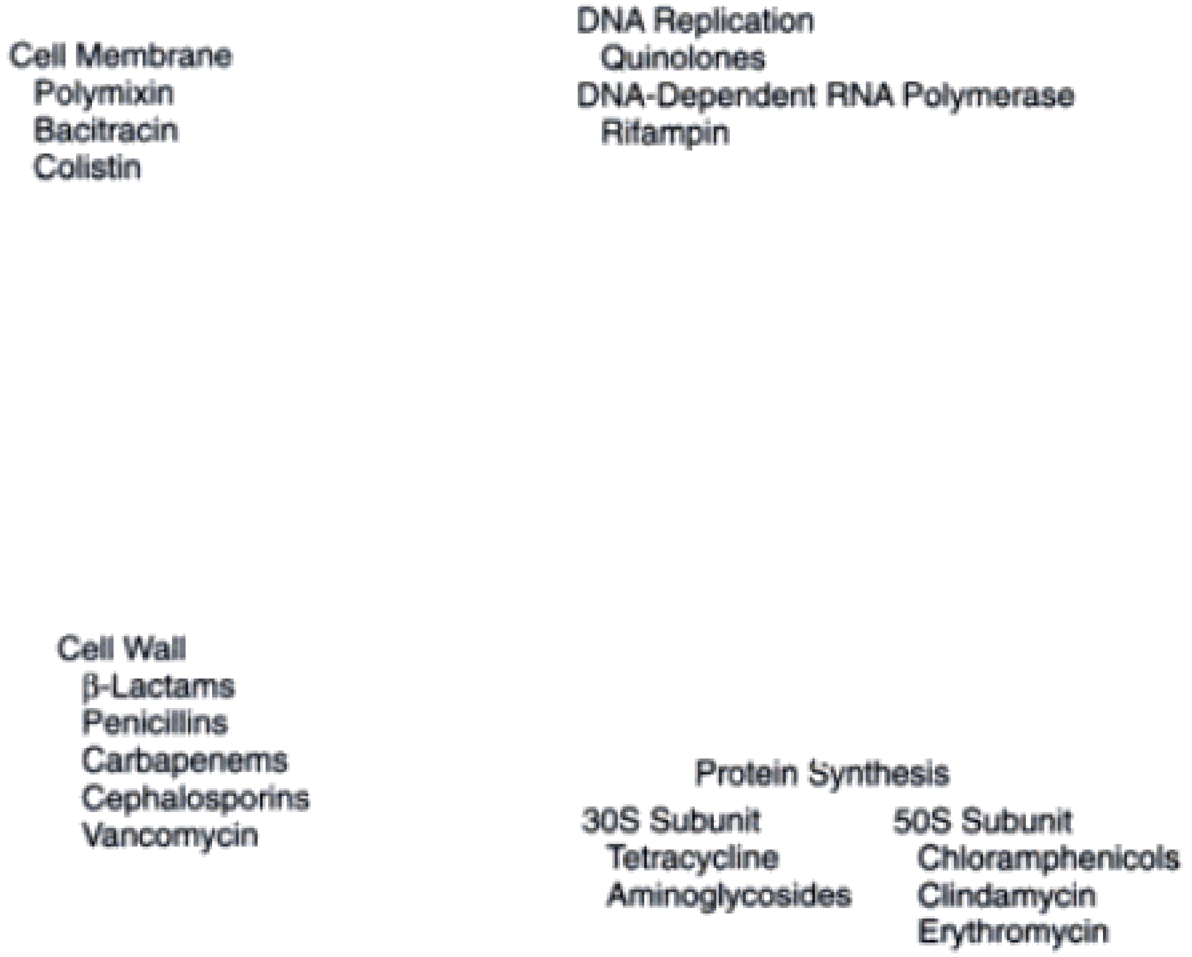

Figure 9–1. Drug mechanisms of action determine drug efficacy, bactericidal or bacteriostatic effects, mechanisms of bacterial resistance, and appropriateness of combination therapy. Occasionally, the mechanism of drug action predicts the mechanism of host toxicity.

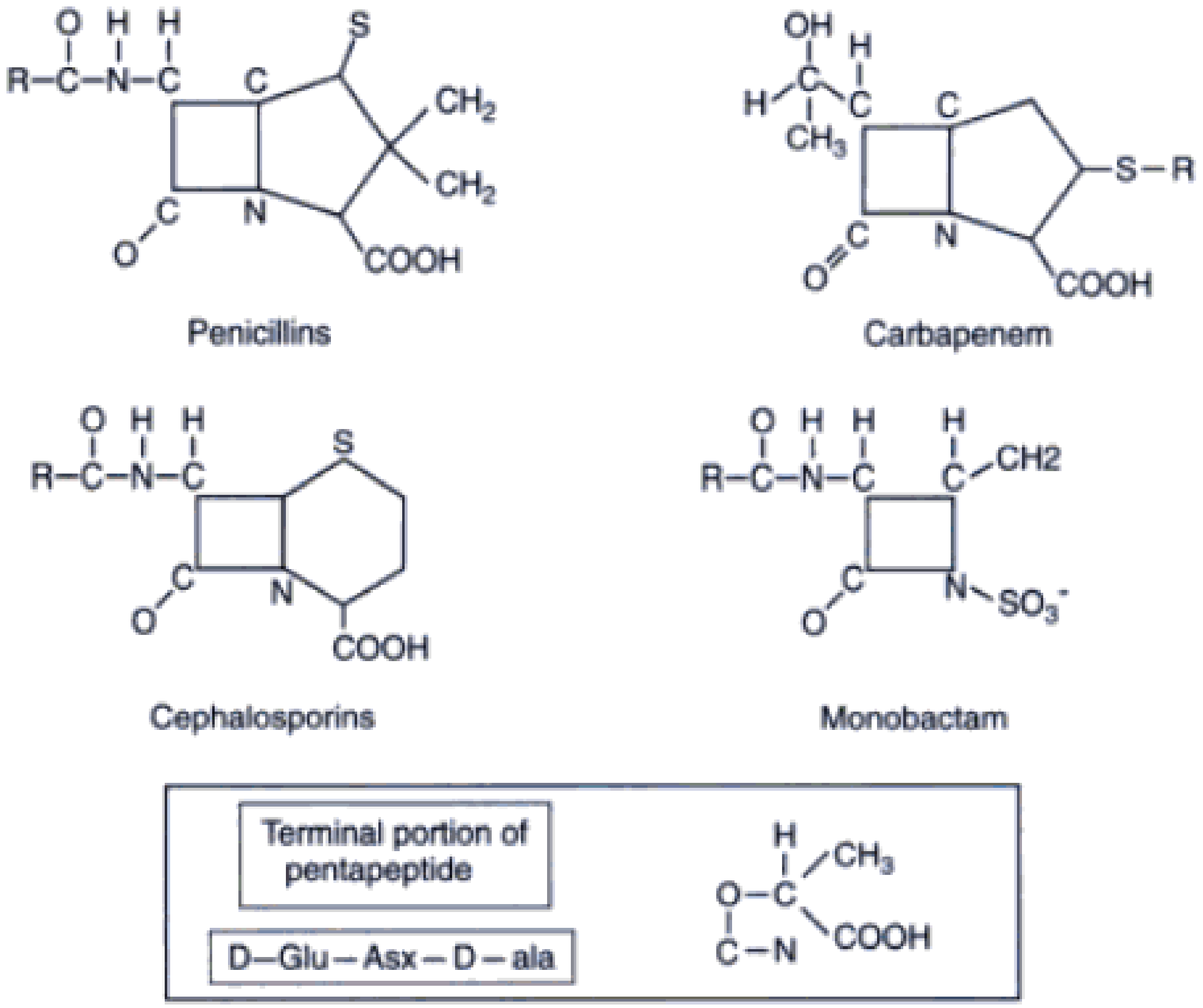

Figure 9–2. β-Lactam antibiotics include the penicillins and cephalosporins. The β-lactam ring (boxed) mimics the substrate of the transpeptidase enzyme (penicillin-binding protein), the terminal portion of Asp-Ala-Asp-Ala. The box is the target of β-lactamase destruction. Penicillins have an adjacent five-member ring, cephalosporins a seven-member ring.

lar to the D-Ala-D-Ala terminus of the pentapeptide and inactivates the transpeptidase enzyme (see Fig. 9–3). In an actively growing cell, the organism continues both cell wall synthesis and cell wall degradation by bacterial autolysins. Degradation continues, and, in the face of impaired synthesis, the bacterial cell wall loses rigidity and becomes permeable to the surrounding environment. In an isotonic (to the host; hypotonic to the organism) environment, movement of fluid into the hypertonic bacterial cell results in osmotic lysis.

The differences in the spectrum of the β-lactam antibiotics probably reflects, in part, differences in affinity of the drugs for the various PBPs (transpeptidases). Although β-lactams are very effective antibiotics, their unique mechanism of action renders them susceptible to failure in certain conditions, independent of bacterial resistance. Efficacy is reduced in a hypertonic environment because osmotic lysis may not occur. Impaired autolysin activity, which may occur in slowly growing bacteria, may result in the loss of the bactericidal effect of the β-lactam antibiotic.

Spectrum of Activity

The penicillins include natural, semisynthetic, and synthetic drugs (Table 9–3). Penicillin G, a natural penicillin, pro-

Figure 9–3. The antibacterial mechanism of action of the β-lactams. The pentapeptide containing the D-Ala-D-Ala terminus provides the cross-linking of the strands of the cell wall, which are critical to rigidity. Two types of penicillin-binding proteins are located in the cell wall of bacteria. Transpeptidase enzymes are responsible for catalyzing the cross-bridging between the pentapeptides; β-lactamase penicillin-binding proteins destroy the β-lactam antibiotics. In the case of gram-positive organisms, the β-lactases are both located in the cell wall and secreted into the environment.

Table 9–3. Doses of Antimicrobials

Drug	Dose (mg/kg)	Interval (hours)	Route[1]
Amikacin	10 (D), 7 (C)	12	IV,[1] IM
	20 (D), 15 (C)	24	IV,[1] IM
Amoxicillin	11–22	8–12	PO, SC, IM
Amoxicillin with clavulanic acid*	10–20	8–12	PO
Ampicillin	10–20[2]	8	PO
	20–30[3]	8	PO
	6.6	8–12	PO
	5[2]	8–12	SC
	10[3]	8	SC
	5[2]	6–8	SC
	10[3]	6	IV
Azithromycin	5–10 (up to 40) (D)	12–24	PO
	5 (C)	24–48	PO
	5 (C)	7 days	PO (prophylaxis)
Carbenicillin indanyl	55–100 (UTI only)	8	IV; PO (indanyl only)
Cefaclor (2nd)	13	8	PO
Cefadroxil (1st)	22	12 (D)–24 (C)	PO
	10[2]	8–12	PO
	30[3]	8	PO
Cefamandole	6–40	6–8	IM, IV
Cefazolin (1st)	15–35	4–8	IV, IM, SC
	10[2]	4–8	IV, IM, SC
	30[3]	4–8	IV, IM, SC
Cefepime (4th)	50	8	IM, IV
Cefixime (3rd)	5–12.5 (D)	12–24	PO
Cefmetazole	20 (D)	6–12	IV
Cefoperazone (3rd)	22 (D)	6–12	IV
Cefoxitin (2nd)	22–30	6	IV, IM, SC
	10[2]	6–8	IV, IM, SC
	20[3]	6–8	IV, IM, SC
Cefotaxime (3rd)	20–80	6	IV, IM
Cefotetan (2nd)	30	8	IV, SC
Cefpodoxime (3rd)	5–10	12–24	PO
Ceftazidime (3rd)	15–30	6–12	IM, IV
Ceftiofur (3rd)	2.2–4.4	12–24	SC
Ceftizoxime (3rd)	25–50	8–12	IM, IV
Ceftriaxone (3rd)	15–50	12–24	IM, IV
Cefuroxime (2nd)	10	12	PO
Cephalexin (1st)	10–60	6–8	PO
	22[2]	8–12	PO
	30[3]	8	PO
Cephalothin (1st)	15–35	6–8	IV, SC, IV
	20[2]	8–12	IV, SC, IV
	40[3]	8	IV, SC, IV
Cephapirin (1st)	30	4–8	IM, SC, IV
Chloramphenicol	50–55 (D)	6–8	PO
	25–50	6–8	IV, IM, SC
	50 mg/cat (C)	12	IV, IM, SC, PO, tablet
	70 mg/cat	12	PO, suspension
Ciprofloxacin	5–30	12–24	IV[2]
	10–40	12–24	PO
Clarithromycin	5–10	12	PO
Cloxacillin	20–40	8	IV, IM, PO
Clindamycin	5 (D)	12	PO
	11–20 (D[4])	12 (PO)–24 (SC)	PO, SC
	11 (C)	12	PO
	25–50[5]	24	PO
Clofazimine	4–8	24	PO
Dapsone	1.1	8–12	PO
Dicloxacillin	10–50	8	PO
Difloxacin	5–10	24	PO
Doxycycline	5–10	12–24	PO
	5	24	IV
Enrofloxacin	2.5–5	12–24	PO, SC
	5–10[6]	12–24	PO, SC, IV[6, 7]
	20	24	PO, SC, IV[6, 7]
Erythromycin	10–20	8	PO
Ethambutol	15–25	24–72	PO
Florfenicol	25–50	8 (D), 12 (C)	IM, SC

Table 9–3. Doses of Antimicrobials *Continued*

Drug	Dose (mg/kg)	Interval (hours)	Route[1]
Gentamicin	2–4	8–12	IM, SC, IV
	8–12	24	IV, IM, SC
Hetacillin	11–44	8–12	PO
Imipenem/cilastin	1–7.5	6–8	IM, IV[8]
Isoniazid	10 (D)	24	PO
Kanamycin	5–7.5	8	IM, IV, SC
Lincomycin	15	8	PO
	22	12	PO
	15	12	IM, IV[8]
	22	24	IM, IV[8]
Marbofloxacin	1.25–2.5	24	PO
Methanamine mandelate	16.5 (D only)	24	PO
Metronidazole	10	8–12	IV
	10–30	8–12	PO
Minocycline	3	12	PO
Neomycin	10–15	6–24	PO
Nitrofurantoin	2.2–4.4	6–24	PO
Novobiocin	10–22	8–12	PO
Ofloxacin	2.5–10	12–24	PO
Orbifloxacin	2.5–7.5	14	PO
Oxacillin	20–40	8	PO
	5–10	6–8	IV
Oxytetracycline	10–25	8	PO, IV
	20	7 days (repositol)	IM
Penicillin G			
Na+ or K+ salt	20,000–60,000	4–6	IV
Procaine	22,000–100,000[9]	8–12	IM, SC
Benzathine	40,000–50,000[10]	5 days	IM, SC
Penicillin V	5.5–11	6–8	PO
Piperacillin	25–50	8	IV, IM, SC
Rifampin	5–20	12–24	PO
Roxithromycin	15 (D)	24	PO
Streptomycin	10–20	12	IM
Sulfadiazine/trimethoprim	30	12–24	PO, SC, IM
	15	12	IV
Sulfadimethoxine/ormetroprim	55	First dose	PO
	27.5	12–24	PO
Teicoplanin	3–12	12	IV, IM, SC
Tetracycline	13.75	6	PO
	20	8	PO
Ticarcillin with or without clavulanic acid	40–50[11]	6–8	IV
	75–100[12]	6–8	IV
Tobramycin	4–6	8–12	IV, IM, SC
Vancomycin	3 (D)	8–12	PO
	10–20	6–12	IV

Abbreviations: C = cat; D = dog; IM = intramuscular; IV = intravenous; PO = oral; SC = subcutaneous; UTI = urinary tract infection.

[1] Slow IV infusion recommended for most drugs.

[2] For gram-positivie infections.

[3] For gram-negative infections.

[4] For osteomyelitis (labeled dose).

[5] For toxoplasmosis infections in cats.

[6] Higher dose recommended for selected *Staphylococcus aureus* and most *Pseudomonas aeruginosa* infections. Dose may be insufficient for organisms with a high MIC that are close to the break point.

[7] SC solution can be given IV if diluted in saline and administered as slow IV bolus.

[8] Dilution in saline recommmended before IV administration; follow directions on package insert.

[9] Dose is listed in units per kg body weight.

[10] Slow-release preparations may not yield effective concentrations for organisms with high MIC.

[11] For susceptible non-*Pseudomonas* spp.

[12] For susceptible *Pseudomonas* spp.

vides a basis for the definition of the international unit (IU) of penicillin: Each unit contains 0.6 mg of the international pure crystalline sodium penicillin. As a group, the natural penicillins are not very stable. Hydrolysis causes degradation of the β-lactam ring and can occur when penicillins are combined with other solutions. Oral absorption is limited by their instability (Vaden and Riviere, 1995). The spectrum of activity of β-lactam antibiotics varies (see Table 9–2). Penicillin G, a natural antibiotic, is effective against gram-positive cocci and both gram-negative and gram-positive anaerobes, but it is β-lactamase sensitive (Neu, 1994). The gram-negative spectrum of penicillin G is limited but includes *Pasteurella multocida*. Penicillin V is an orally bioavailable natural penicillin, but its antimicrobial efficacy is reduced (Vaden and Riviere, 1995). β-Lactamase-resistant penicillins include dicloxacillin, cloxacillin, methicillin, and oxacillin. These drugs are effective against gram-positive organisms such as *Staphylococcus* species. Their efficacy against other gram-positive and selected gram-negative organisms is fair to good, but they are generally not as effective as are other penicillins.

The spectrum of the β-lactams was increased with the production of the semisynthetic aminopenicillins. Amoxicillin and ampicillin (aminopenicillins) are considered "broad-spectrum" drugs. The anaerobic and gram-positive spectrum of penicillin G is maintained (although the aminopenicillins are slightly less efficacious against anaerobes). In addition, many gram-negative organisms are added to the spectrum, including *Escherichia coli, Pasteurella*, some *Proteus* species, *Klebsiella*, and selected others. *Serratia, Enterobacter*, and *Pseudomonas* are gram-negative organisms that are not, however, included in the spectrum of the aminopenicillins. The aminopenicillins are less effective against *Bacteroides fragilis* (Vaden and Riviere, 1995). Like penicillin, the aminopenicillins are β-lactamase sensitive. Combination with a β-lactamase protector (e.g., clavulanic acid or sulbactam) improves efficacy toward susceptible organisms such as *E. coli, Klebsiella* species, and some *Proteus* species. β-Lactamase protection does not, however, increase the spectrum of amoxicillin; *Pseudomonas* species and other gram-negative organisms remain resistant (Bush et al., 1989; Vaden and Riviere, 1995).

A fourth class of penicillins includes the extended spectrum antibiotics. These drugs remain effective against gram-positive and anaerobic organisms, and the gram-negative spectrum is extended to include *Pseudomonas aeruginosa, Serratia, Proteus* species and some *Klebsiella* species, *Shigella* species, and *Enterobacter* species. Examples include carbenicillin; ticarcillin, which has two to four times higher activity toward *Pseudomonas* than carbenicillin; and piperacillin, which has the highest antipseudomonal activity (Neu, 1994; Bush et al., 1989; Brown, 1988; Papich, 1988). The extended spectrum penicillins are effective against anaerobic organisms, although they may be less effective than the natural penicillins. They are, however, effective against *B. fragilis* (Vaden and Riviere, 1995). The extended spectrum penicillins are β-lactamase sensitive; however, a ticarcillin/clavulanic acid combination product is available.

Imipenem is one of the newest members of the β-lactam penicillins and is classified as a carbepenem β-lactam antibiotic (Sobel, 1989). It is prepared in combination with cilastatin, which inhibits renal tubular degradation of imipenem. As a result, drug half-life is prolonged, and the formation of potentially nephrotoxic metabolites is reduced. Imipenem has one of the broadest antimicrobial spectrums available, including *Pseudomonas* species. Imipenem is very resistant to β-lactamase destruction. An advantage of this drug is its very low minimum inhibitory concentration (MIC; 0.05 to 2 μg/mL) for most organisms. Although the drug has not been studied in dogs or cats, veterinary use appears to be successful.

The cephalosporins (see Fig. 9–3) are subcategorized as first, second, and third generation (see Table 9–1) (Donowitz, 1989; Caprile, 1988). This categorization is primarily of chronologic importance. Although generalizations regarding the spectrum of activity of each generation can be made, either the package insert or culture and susceptibility data should be considered for individual drugs in each class. Cephalothin is the drug used by the National Committee for Clinical Laboratory Standards (NCCLS) as an indicator for susceptibility for the first-generation cephalosporins, but even within generations variability in efficacy among the drugs may result in therapeutic failure (Vaden and Riviere, 1995). The spectrum of the first-generation cephalosporins is similar to that of the aminopenicillins (Vaden and Riviere, 1995). First-generation cephalosporins such as cefazolin, cephalothin, and cephalexin are active against gram-positive and gram-negative organisms such as *E. coli, Klebsiella pneumoniae*, and *Proteus mirabilis*. Among the first-generation drugs, cefazolin has better efficacy against gram-negative organisms but poorer efficacy against *Staphylococcus* species (Vaden and Riviere, 1995; Neu, 1994). Cephalexin is less active against staphylococci; it is more β-lactamase stable (Neu, 1994). The anaerobic spectrum of the first-generation cephalosporins is fair. Because cephalosporins are more resistant to β-lactamases, they are generally more effective than penicillins against *Staphylococcus* species.

The second-generation cephalosporins, cefamandole, cefaclor, cefoxitin, and others, are characterized by enhanced activity toward *Enterobacter* species, some *Proteus* species, *E. coli*, and *Klebsiella* species (Neu, 1994). Third-generation cephalosporins (cefotaxime, ceftazidime, and cefoperazone, and the oxa-β-lactam moxalactam) are generally reserved for serious gram-negative infections caused by *P. aeruginosa, Enterobacter* species, and *Serratia* species. Not all third-generation cephalosporins are, however, effective against *P. aeruginosa* (Vaden and Riviere, 1995). In contrast to penicillins, in which anaerobic and gram-positive spectra were maintained as the spectrum was extended, the second-generation and third-generation cephalosporins are often less effective than first-generation drugs against gram-positive and anaerobic organisms. An exception is cefoxitin, which has an excellent anaerobic spectrum, particularly against *Bacteroides* species (Neu, 1994; Donowitz, 1989), although it is less effective than first-generation drugs against gram-positive organisms. Selected third-generation cephalosporins (e.g., cefotaxime) are effective against anaerobic organisms, whereas others (e.g., ceftazidime and ceftriaxone) are not; the spectrum of each product should be reviewed before use.

Ceftiofur is a third-generation cephalosporin recently approved for use for canine urinary tract infections. The antimicrobial spectrum of ceftiofur includes selected gram-positive (*Streptococcus* species and *Corynebacterium* species), gram-negative (*Pasteurella, E. coli*, and *Salmonella* species), and anaerobic organisms. Ceftiofur is effective against many staphylococcal organisms; however, selection against *Staphylococcus* should be based on culture and susceptibility data (Vaden and Riviere, 1995). Unlike some other third-generation cephalosporins, the spectrum of ceftiofur does not include virulent gram-negative organisms such as *Pseudomonas* species. Ceftiofur also stands out because its major metabolite is active, thus prolonging its efficacy.

Resistance

A major mechanism of bacterial resistance to the β-lactam antibiotics is inactivation by bacterial β-lactamases. These enzymes, another type of PBP, are the result of either chromosomal mutations, particularly in gram-positive organisms, or plasmid-mediated resistance in both gram-positive and gram-negative organisms. β-lactamases are either constitutive, already present in the cell wall (particularly in gram-negative organisms), or are induced by the presence of the antimicrobial drug (in both gram-negative and gram-positive organisms). Many gram-negative, gram-positive, and anaerobic organisms are capable of producing β-lactamases. The type of enzyme depends on the organism: Some microbes produce β-lactamases directed toward only penicillins, some toward cephalosporins, and others toward both classes of β-lactam antibiotics. Gram-negative bacteria secrete β-lactamases into the periplasmic space such that they are strategically placed before the antibiotic can penetrate the cell wall (Vaden and Riviere, 1995).

The β-lactams are variably susceptible to destruction by β-lactamases (see Table 9–2). The cephalosporins are generally more resistant to β-lactamases, particularly those produced by *Staphylococcus* species. Selected synthetic antimicrobials are resistant to the effects of β-lactamase, including most third-generation cephalosporins and imipenem. The semisynthetic dicloxacillin (and oxacillin) is β-lactamase resistant, whereas the aminopenicillins and extended spectrum penicillins are β-lactamase susceptible. The combination of β-lactam antibiotics with drugs (e.g., clavulanic acid and sulbactam) that inhibit the activity of β-lactamase enzymes increases the efficacy (but not the spectrum) of susceptible organisms (see Tables 9–1 and 9–2). Other mechanisms of resistance to the β-lactamases include changes in porin size with failure to reach the PBP by gram-negative (and especially *Pseudomonas aeruginosa*) organisms and a change in the PBP structure such that antibiotic binding does not occur (e.g., staphylococcal organisms and penicillins; enterococcal organisms and cephalosporins). Interestingly, drugs that inhibit protein synthesis (e.g., chloramphenicol) may enhance efficacy of some penicillins against some organisms by decreasing β-lactamase production.

Pharmacokinetics

The β-lactams are weak acids, which favor oral absorption. Many of the β-lactam antibiotics are, however, destroyed by the acidity of the gastrointestinal tract and thus cannot be given orally. Exceptions include penicillin V, dicloxacillin, the aminopenicillins (ampicillin and amoxicillin, including combinations with clavulanic acid), and the first-generation and third-generation cephalosporins cephalothin and cefadroxil, respectively. Carbenicillin is orally bioavailable only as the indanyl form, and even then effective concentrations can only be achieved in urine. For the aminopenicillins, the oral bioavailability of amoxicillin is greater than that of ampicillin and, unlike ampicillin, is not impaired by the presence of food (Neu, 1994). The oral bioavailability of the cephalosporins is also variable among drugs and species (Neu, 1994; Vaden and Riviere, 1995).

Many β-lactams are available as intravenous (IV) or parenteral preparations. Absorption from parenteral sites tends to be rapid and complete, with the exception of products that are specifically formulated to allow slow release. Preparations of penicillin G intended for intramuscular (IM) use (e.g., procaine and benzathine) may be prepared as esters, which hydrolyze at variable rates and thus prolong absorption. Procaine penicillin is absorbed for at least 24 hours and benzathine penicillin for approximately 120 hours (Vaden and Riviere, 1995). Although drug levels may persist longer in circulation with these preparations, therapeutic concentrations may not be achieved for organisms with sufficiently high MICs, and caution is recommended with the use of slow-release products.

Distribution of β-lactams is limited to extracellular fluid, but adequate concentrations can usually be achieved in many tissues because most infections are extracellular in location (Vaden and Riviere, 1995; Neu, 1994). Because β-lactams are concentrated in the urine, effective concentrations may be achieved in urine even though the MIC might suggest intermediate or medium susceptibility. Penicillins and cephalosporins do not traverse mammary, prostatic, or blood-brain barriers well. An exception is imipenem, but not antipseudomonal penicillins such as ticarcillin and piperacillin. Imipenem can reach effective concentrations in the brain. Inflammation increases the penetration of many penicillins. For example, cefuroxime, cefotaxime, ceftriaxone, and ceftazidime can reach therapeutic concentrations when the cerebral spinal fluid (CSF) is inflamed (Vaden and Riviere, 1995). Inflammation may also increase β-lactam penetration of abscesses and pleural, peritoneal, and synovial fluids.

Cephalosporins are also widely distributed throughout most extracellular body fluids, including kidneys, lungs, joints, bone, soft tissues, and bile (Caprile, 1988; Neu, 1994; Donowitz, 1989). First-generation and second-generation cephalosporins should not be used for central nervous system (CNS) infections because many are destroyed by local enzymes or transported out of the CNS. Drug elimination half-life tends to be less than 2 to 4 hours.

The β-lactam antibiotic drugs are eliminated by active tubular secretion in the renal tubules. With the exception of hetacillin, hepatic metabolism does not play a role in the elimination of the penicillins. Hetacillin is an "ampicillin pro-drug" prepared by reacting ampicillin with acetone; the reaction reverses when administered as an aqueous solution (Vaden and Riviere, 1995). Hetacillin may more easily penetrate the prostate than ampicillin, and subsequent metabolism in the prostate to ampicillin may result in therapeutic concentrations of ampicillin, although this has not been proved clinically. Imipenem is degraded to inactive metabolites in the kidney. Reabsorption from the urine is facilitated by an acid urinary pH. Some cephalosporins are eliminated in the urine after deacetylation by the liver. Examples include cephalothin, cephapirin, cefotaxime, and ceftiofur. Deacetylation of ceftiofur results in an active metabolite. Ceftriaxone and cefoperazone are eliminated in the bile in humans and appear to be at least partially eliminated in the bile in dogs (Vaden and Riviere, 1995).

Adverse Effects

The β-lactam antibiotics are very safe. Hypersensitivity is an infrequent reaction and occurs less commonly with cephalosporins. Penicilloic acid is the more likely mediator of hypersensitivity reactions; it is generated from the activity of several enzymes of variable sources. Thrombocytopenia has been reported to occur with some members of this class.

Therapeutic Use

The broad spectrum and wide safety margin of the β-lactam antibiotics lead to their common use. Caution is recommended, however, when they are used to treat complicated infections without the benefit of culture and susceptibility data. Resistance develops relatively rapidly, and the drugs are not characterized by an excellent distribution pattern. The narrow spectrum of natural penicillin limits its use as the drug of choice to treat anaerobic infections, and its availability as IV solutions results in its combination with other antimicrobials in the case of life-threatening but susceptible infections. Use of β-lactamase-protected penicillins such as dicloxacillin is limited by cost and a relatively narrow spectrum.

The aminopenicillins tend to be first-choice antimicrobials for empirical antibiotic therapy of most body systems with perhaps the CNS as an exception. Of the aminopenicillins, amoxicillin is preferred for oral administration because of its enhanced bioavailability and perhaps slightly better efficacy. Because amoxicillin is susceptible to β-lactamase destruction, combining amoxicillin with clavulanic acid should be considered for any infection that is complicated, including infections that occur in difficult to penetrate tissues and infections associated with large bacterial inoculums.

Use of the extended spectrum penicillins tends to be limited to complicated infections; empirical therapy for life-threatening infections for which broad coverage is desired (including prophylaxis in the immunocompromised patient); or infections for which culture and susceptibility data are available. Because the extended penicillins are susceptible to β-lactamase destruction, combination with a β-lactamase protector (e.g., ticarcillin and clavulanic acid) or use of imipenem—which is inherently more resistant to β-lactamase destruction—should be considered. Imipenem should be considered before other β-lactams for treatment of infections associated with endotoxemia because this drug is associated with the least endotoxin release.

The first-generation cephalosporins are excellent first-choice antibiotics for many infections, including urinary, skin, and respiratory tract infections. Their relative resistance to β-lactamases produced by *Staphylococcus* leads to their frequent empirical selection for infections in which *Staphylococcus* is assumed to be involved. Their efficacy against *Staphylococcus* as well as against many gram-negative organisms leads to their selection for surgical prophylaxis. Of the second-generation cephalosporins, cefoxitin should be considered for empirical therapy requiring a broad-spectrum antimicrobial. With the exception of *P. aeruginosa*, cefoxitin is effective against most other organisms. The use of other second-generation and the third-generation cephalosporins is probably best based on culture and susceptibility data because the spectra of these drugs are so variable.

β-Lactams should be the first drugs considered for combination antimicrobial therapy. Their unique mechanism of action facilitates movement of other drugs into bacteria, which should facilitate efficacy of other antimicrobials that are more toxic than penicillins. The risk of resistance should also be reduced as antimicrobial movement into the cell is improved. β-Lactams are combined with drugs effective against gram-negative organisms when broad-spectrum therapy is needed as in the case of life-threatening infections for which the causative organisms are not known; polymicrobial infections involving anaerobes and aerobes; or gram-positive and gram-negative organisms.

AMINOGLYCOSIDES

Despite their potential nephrotoxicity, aminoglycosides remain the cornerstone of aerobic gram-negative therapy in many complicated or serious infections. Minor differences in the chemical structures of these drugs lead to differences in efficacy and toxicity. Clinically useful aminoglycosides include neomycin, gentamicin, amikacin, and streptomycin (or dihydrostreptomycin). Newer aminoglycosides include tobramycin and netilmicin.

Mechanism of Action

Aminoglycoside compounds are composed of an amino sugar linked through glycosidic bonds to an amino cylitol (Neu, 1994; Riviere and Spoo, 1995). They vary in the amino sugar and the specific number and location of the amine groups (Fig. 9–4). Aminoglycosides must be actively transported into the bacterial cell. Their efficacy depends on a high oxygen tension in the environment.

Transport of aminoglycosides into the bacterial cell begins with an initial ionic interaction between the positively charged aminoglycoside and the negative bacterial cell membrane. An acidic environment should facilitate uptake of these basic drugs by increasing the attraction of the cell membrane and the aminoglycoside. Ions such as calcium and magnesium in the lipopolysaccharide membrane help prevent aminoglycoside transport into bacterial cells (and renal tubular cells) because the cationic charges repel the drugs, thus decreasing interaction between the drugs and the lipopolysaccharide membrane. Removal of the cations (such as with EDTA or in the hypocalcemic patient) facilitates aminoglycoside movement into the cell (Neu, 1994; Riviere and Spoo, 1995).

Because oxygen is needed for active transport, anaerobic organisms are inherently resistant to aminoglycosides, and aminoglycosides are ineffective against facultative aerobes located in an anaerobic environment. Once inside the cell, aminoglycosides bind to both the 30S and 50S subunits of ribosomes (Fig. 9–5). Binding is so effective that polyribosome formation is prevented, and protein synthesis is impaired due to altered synthesis and misreading. Thus, in contrast to bacteriostatic drugs, which bind to single ribosomes, the aminoglycosides are more likely to achieve bactericidal concentrations safely in animals.

Spectrum of Activity

The spectrum of activity of aminoglycosides (see Table 9–2) includes most aerobic gram-negative bacteria, particu-

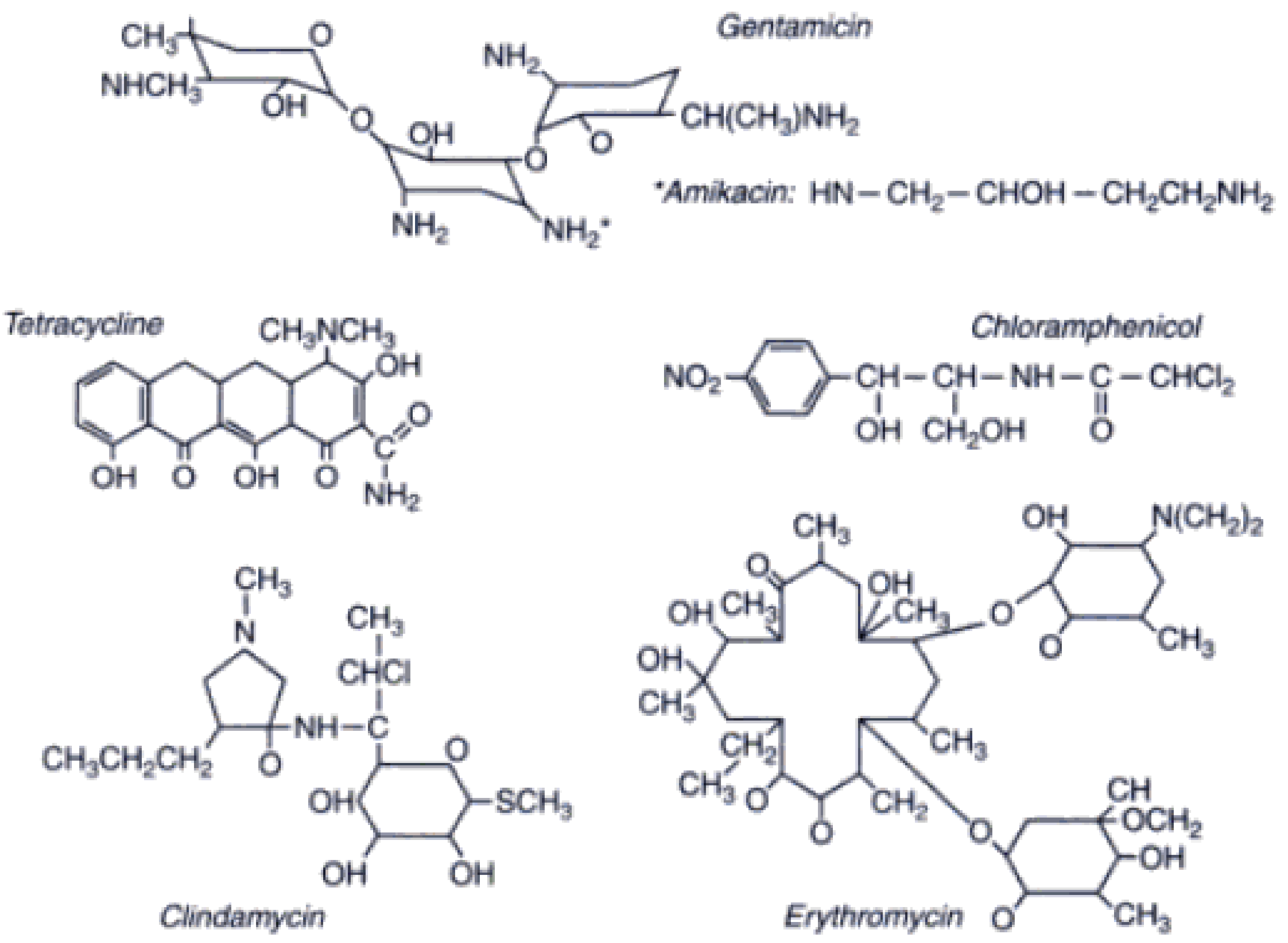

Figure 9–4. Chemical structures of ribosomal inhibitors.

larly *E. coli, K. pneumoniae, P. aeruginosa, Proteus* species, and *Serratia* species (Neu, 1994; Riviere and Spoo, 1995; Roudebush and Fales, 1982; Brown, 1988). These drugs are also effective against selective aerobic gram-positives organisms, most notably *Staphylococcus* species. Gentamicin, tobramycin, and amikacin are particularly effective against *P. aeruginosa, Proteus* species, and *Serratia* species; gentamicin is the least effective of the three against *P. aeruginosa*, but most effective against *Serratia marcescens*. Amikacin is most effective against *P. aeruginosa*. With the exception of *Pseudomonas* species (an obligate aerobe), these organisms are facultative anaerobes and, if cultured aerobically from an anaerobic environment, may fail to respond to aminoglycoside therapy in the patient. The aminoglycosides are also effective against *Nocardia* and selected atypical mycobacterial organisms.

Bactericidal efficacy and the postantibiotic effect of aminoglycosides correlate with peak concentrations, which ideally should be at least four to eight times the MIC of the target organism (Maller et al., 1993; Nördstrom et al.,

Figure 9–5. The mechanism of action of ribosomal inhibitors. The aminoglycosides inhibit ribosomal initiation, effectively converting the multiple ribosomal actions (polyribosome) to a monoribosome function. Tetracyclines bind to the 30S subunit of ribosomes, preventing the translocation of the amino acid from transfer RNA (tRNA) to the codon of messenger RNA (mRNA). Chloramphenicol and erythromycin prevent the transfer of peptides by binding to the 50S subunit. Erythromycin and clindamycin prevent translocation of the peptide. Drugs that act at the same site should not be used in combination.

1990; Powell et al., 1983; Blaser, 1991; Reiner et al., 1978). In contrast, the toxicity of aminoglycosides is correlated with trough concentrations (see later discussion of the adverse effects of aminoglycosides). For treatment of selected susceptible bacteria, once daily administration of aminoglycosides has been shown to be both clinically (Vanhaeverbeek et al., 1993; Powell et al., 1983; Reiner et al., 1978) and experimentally (Powell et al., 1983; Blaser, 1991; Blaser et al., 1985) equal to or more efficacious and safer than the traditional frequency of administration (i.e., two to three times daily). The appropriateness of this dosing method may vary with the organism and the immunocompetence of the patient.

Resistance

Besides the inherent resistance of anaerobic organisms (due to decreased active transport), resistance to aminoglycosides is acquired by altered porin size in the gram-negative organism and, more commonly, destruction by microbial enzymes inside the cell. Target sites of destruction by these enzymes are harder to reach with amikacin; hence amikacin is less vulnerable to resistance than are the other aminoglycosides (Neu, 1994; Roudebush and Fales, 1982).

Pharmacokinetics

The aminoglycosides are water-soluble weak bases, and as such they are poorly absorbed from the gastrointestinal tract. An exception might occur in very young animals (still absorbing colostrum) or in the presence of inflammatory gastrointestinal disease (Riviere and Spoo, 1995). Aminoglycosides must be administered topically (including aerosolization) or parenterally but can be used orally for bacterial cleansing of the gastrointestinal tract. Absorption of aminoglycosides from IM or subcutaneous (SC) injections is generally good, although variability occurs. In dogs, gentamicin is 95% bioavailable after IM injection but only 68% bioavailable in cats. Amikacin is 90% to 100% bioavailable in dogs and cats after IM or SC injections. Generally, peak concentration after SC administration is less than that after IM administration, and both are less than that after IV administration (Boothe, unpublished data). Kanamycin, which is structurally very similar to amikacin, behaves similar to amikacin (Riviere and Spoo, 1995).

Although aminoglycosides are distributed to extracellular fluids, their penetration into many tissues is considered poor (Boothe, unpublished data). Therapeutic concentrations can be attained in synovia and in pleural and peritoneal fluid, particularly if membranes are inflamed. Therapeutic concentrations generally are not attained in CSF, ocular fluids, bile, milk, and prostatic secretions. Aminoglycosides are actively accumulated by renal tubular cells, but in small animals this is of more relevance to toxicity than to efficacy. In addition to anaerobic environments, the efficacy of aminoglycosides is reduced in an acidic environment such as might occur in the urine, ascitic fluid, and abscesses.

The aminoglycosides are eliminated by glomerular filtration, which is a relatively inefficient process. Alkaline urine pH facilitates reabsorption. Drug elimination half-life is generally less than 2 to 4 hours. The disposition of aminoglycosides varies among animals, primarily because of differences in glomerular filtration rates. Elimination is slower in larger animals as glomerular filtration rate increases with body size. Dosing based on metabolic rate normalizes the rate of elimination and might be considered in patients predisposed to aminoglycoside nephrotoxicity.

The disposition of aminoglycosides differs among ages. Plasma drug concentrations are less in the neonate and pediatric patient because greater total body water and extracellular fluid compartments increase the volume of distribution of the drugs from 0.25 to 0.35 L/kg. Renal clearance of aminoglycosides is less. Thus, for young animals, the dose of aminoglycosides should be increased, but the interval should be prolonged (although not necessarily beyond 24 hours). Disposition is also altered by disease. Dehydration and obesity increase plasma drug concentrations; intensive fluid therapy, ascites, or other syndromes associated with fluid accumulation and endotoxemia decrease plasma aminoglycoside therapy (Riviere and Spoo, 1995). Elimination is impaired in the patient with renal disease; dosing regimens are usually modified by lengthening the interval based on serum creatinine concentration.

Adverse Effects

The aminoglycosides induce a glomerular and (principally) tubular nephrotoxicity that is largely reversible unless allowed to progress to an irreversible state. Toxicity results from active uptake into the renal tubular cell and disruption of cellular lysosomes (Fig. 9–6). As with uptake into the bacterial cell, nephrotoxicity may be related to the number of positively charged amino groups on the drugs (Neu, 1994). An acidic local pH may enhance uptake by ionizing the aminoglycoside. Of the clinically used aminoglycosides, neomycin is the most nephrotoxic and dihydrostreptomycin the least. The nephrotoxicities of the other aminoglycosides are between these two extremes. Uptake of aminoglycosides may be related to the amount of phosphatidylinositol in the cell membrane; the amount of this phospholipid is disproportionately higher in renal cortex and cochlear tissues (Riviere and Spoo, 1995). Impaired synthesis of protective vasodilatory renal prostaglandins by the aminoglycoside may be important to the development of nephrotoxicity.

Reversible renal impairment occurs in up to 25% of human patients receiving aminoglycosides for more than 3 days. The exact mechanism of aminoglycoside-induced nephrotoxicity is not known. Toxicity begins as the anionic phospholipids of the renal tubular cell membranes attract and bind the cationically charged drugs. This attraction can be competitively inhibited by divalent cations or decreased in an alkaline urine. Aminoglycosides are then actively accumulated into the cell by pinocytosis; intracellular accumulation may result in concentrations greater than 50-fold of that in plasma. Inside renal tubular cells, aminoglycosides are sequestered in lysosomes, which appear morphologically as myeloid bodies. The drugs are slowly eliminated back into the urine as myeloid bodies containing drug, RNA, and DNA after the tubular cell dies. The cause of tubular cell death remains unclear, although a number of

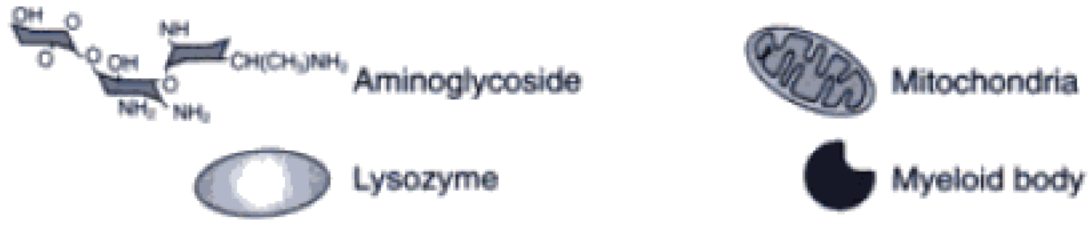

Figure 9–6. Nephrotoxicity of aminoglycosides occurs primarily in the proximal tubular cells. The cationic charge of the drugs is attracted to the anionic charge of the phosopholipids in the cell membrane. Ionization (as would occur in an acidic environment) facilitates binding. The drug is actively accumulated in the cell by pinocytosis. Inside the cell, the drugs accumulate in lysozymes, causing lysosomal disruption and release of myeloid bodies. Mitochondrial function is also impaired. The effects of prostaglandin on renal blood flow may contribute to the toxicity of aminoglycosides.

cellular functions (in addition to lysosomal) are impaired. Mitochondrial respiration is decreased, impairing energy resources of the cell. Again, this may reflect interaction between the drug and mitochondrial cell membrane. Proximal tubular permeability may be impaired both directly as drugs interact with the cell membrane and indirectly as a result of impaired Na^+,K^+-ATPase activity. Aminoglycosides also alter glomerular function perhaps by reducing the number and size of glomerular endothelial cells (Riviere and Spoo, 1995). Finally, phospholipases important for renal prostaglandin synthesis are among the enzymes impaired by aminoglycosides. The initial decrease in glomerular filtration that accompanies aminoglycoside therapy may reflect the inability of the kidney to vasodilate in response to vasoconstrictor actions such as that signaled by angiotensin II (Riviere and Spoo, 1995).

A bimodal course of aminoglycoside-induced nephrotoxicity has been described in the dog, with an initial subclinical phase characterized by a concentrating defect and an azotemic phase. The amount of aminoglycoside necessary to impair renal function has not been determined, in part because different drugs are studied at different doses and intervals. In clinical patients, this amount is likely to further differ because of differences in drug disposition and renal susceptibility to toxicity. In experimental animals, gentamicin at 4 mg/kg every 12 hours in dogs changes urine osmolarity within 7 days and an increase in serum creatinine by 17 days. Urinary prostaglandin E activity decreases before azotemia, which may be responsible for the state of nephrogenic diabetes insipidus. Higher doses of 30 mg/kg administered at 8-hour intervals in dogs results in increases in urine γ-glutamyltransferase within 2 days and serum creatinine within 9 to 12 days. Studies in cats have focused on doses of 35 mg/kg or more at intervals of 12 hours or less (Riviere and Spoo, 1995).

Studies that have focused on aminoglycoside toxicity in dogs and cats have used an interval that ranges from 12 hours to constant IV infusion. Recent studies in dogs (Boothe, unpublished data), people, and experimental models have supported a 24-hour dosing interval (administering the total daily dose once a day) for aminoglycoside therapy. Efficacy and safety at 24-hour dosing intervals appears to be equal to or enhanced (due to a higher inhibitory quotient) compared with efficacy and safety at shorter intervals. Efficacy is enhanced because of the larger inhibitory quotient (plasma drug concentration to MIC). Safety is probably enhanced in the presence of the low plasma drug concentrations that occur during the end of the dosing interval. Renal accumulation of drug decreases, and drug that has been accumulated may actually leave the cell (Riviere and Spoo, 1995).

Some patients (e.g., pediatric dogs <14 days of age, patients with diabetes mellitus or hypothyroidism) are protected against aminoglycoside (gentamicin)-induced nephrotoxicity because renal accumulation in the cortical tissues is limited (Cowan et al., 1980; Brown et al., 1991). The risk of toxicity with aminoglycoside therapy is greater if any condition of the patient depends on renal prostaglandin formation, such as hypotension, shock, endotoxemia, renal or cardiac disease, or with concurrent drug therapy that impairs prostaglandin synthesis, such as nonsteroidal anti-inflammatory drugs (Neu, 1994; Boothe, 1995). Metabolic acidosis (or an acidic urine pH) also predisposes the patient to aminoglycoside nephrotoxicity because drugs are ionized and attracted to the anionic changes of cell membranes (Hsu et al., 1974).

There is no sensitive indicator of renal damage induced by the aminoglycosides. Changes in urine osmolality or sodium fractional clearance typical of the initial subclinical phase may detect a concentrating defect. Release of renal tubular enzymes such as γ-glutamyltransferase into urine have been used experimentally to measure aminoglycoside toxicity. The enzymes increase within several days after damage has begun. Twenty-four–hour sample collection for these procedures is, however, impractical. A change in gentamicin clearance may be the most sensitive indicator of aminoglycoside toxicity (Brown and Garry, 1988; Frazier et al., 1988; Riviere and Spoo, 1995). More recently, measurement of the urine creatine to γ-glutamyltransferase ratio in "spot" samples of urine have proved useful in experimental models of aminoglycoside toxicity (Grauer et al., 1995). Ratios may not, however, change until several days after toxicity has begun (Riviere and Spoo, 1995). A clinical model for predicting aminoglycoside toxicity has been developed in humans.

Changes in aminoglycoside clearance may be the earliest indicator of nephrotoxicity. Renal damage may continue after the drug has been discontinued (or reduced) as the tubules eliminate accumulated drug. Nephrotoxicity is thus best avoided and can be minimized by

1. Using the least nephrotoxic aminoglycoside (i.e., amikacin vs. gentamicin)
2. Ensuring that the patient's hydration status is adequate
3. Modifying dosing regimens based on MIC data, therapeutic drug monitoring, and serum creatine concentrations
4. Maximizing peak plasma drug concentration while ensuring that trough plasma drug concentration drops below 2 μg/mL
5. Using once-daily therapy when appropriate
6. Using combination antimicrobial therapy, particularly with synergistic antibiotics
7. Avoiding use of other nephrotoxic or nephroactive drugs, including antiprostaglandins and furosemide
8. Administration during periods of activity (e.g., normally in dogs).

Ticarcillin can be used to bind aminoglycosides in patients accidentally overdosed, although overdosing may not be a problem if the drug half-life is near normal. The spectrum of the first-generation cephalosporins is similar to that of the aminopenicillins (Vaden and Riviere, 1995). If the source of infection is in the urinary tract, maintaining an alkaline pH will enhance the efficacy of the aminoglycosides while decreasing renal tubular cell uptake of aminoglycosides, presumably due to decreased ionization of the drugs. The role of prostaglandin analogues (e.g., misoprostol) in the prevention or treatment of aminoglycoside toxicity has not yet been established.

Aminoglycosides can cause an irreversible ototoxicity, although this is not likely to occur at therapeutic doses as long as trough concentrations are lower than 2 μg/mL. Like nephrotoxicity, ototoxicity reflects active uptake of the drug by hair cells of the cochlea. Both auditory and vestibular toxicity may occur. As with nephrotoxicity, the ototoxic potential of each drug varies. The drugs typically should not be given to a patient with a perforated eardrum. Aminoglycosides can cause neuromuscular blockade due to impaired calcium release at myoneural junctions. The risk is greater with IV administration, in the presence of hypocalcemia, or when combined with other agents active at the myoneural junction (e.g., anesthetics, skeletal muscle relaxants).

Therapeutic Use

Despite their ability to cause nephrotoxicity, the aminoglycosides remain the most effective drugs for the treatment of serious gram-negative infections. They are also effective against *Staphylococcus, Nocardia, Actinomyces*, and selected mycobacteria. Caution is recommended in their use for infections in tissues that are difficult to penetrate and infections that may be located in an anaerobic environment. Combination therapy and topical therapy (in addition to systemic therapy) should be considered whenever possible for serious or complicated infections. Aminoglycosides cannot be given orally, and their use might be limited to hospitalized patients. Once-daily therapy, however, increases the convenience and safety of aminoglycosides used on an outpatient basis.

Maintaining hydration is probably the single most important means by which the risk of nephrotoxicity can be minimized. Ototoxicity also can be minimized by hydration, and avoidance of topical administration, particularly in the presence of a perforated eardrum. Although gentamicin is the most economical form of aminoglycosides, amikacin should be considered for serious infections because of its improved resistance to antimicrobial destruction and better efficacy against some organisms, including *P. aeruginosa*. The aminoglycosides are often used in combination with other antimicrobials that have a less comprehensive gram-negative spectrum. As with imipenem, the aminoglycosides cause minimal endotoxin release in patients suffering from gram-negative infections associated with a large inoculum (Riviere and Spoo, 1995).

FLUORINATED QUINOLONES

The fluorinated quinolones are a relatively new class of antibiotics. They consist of synthetic agents that are minimally toxic yet are very effective in the treatment of many aerobic gram-negative organisms and selected gram-positive organisms.

Structure-Activity Relationship

The progenitor of the fluorinated quinolones is nalidixic acid. The addition of the fluorine atom and other synthetic changes made to nalidixic acid have resulted in a broader antibacterial spectrum, better tissue distribution, and fewer side effects. All of the fluorinated quinolones contain a carboxylic acid group (which is necessary for antibacterial action) (position 3) and the fluorine atom (position 6); many also contain a piperazine ring (position 7).

Four drugs are currently approved for use in small animals in the United States: enrofloxacin (the first approved, for both dogs and cats), followed rapidly by orbifloxacin (dogs), difloxacin (dogs), and marbofloxacin (dogs; cats expected) (Fig. 9–7). Variations in the chemical structures of these drugs result in few differences in the tissue distribution and spectrum of those products currently approved for use in dogs and cats in the United States. Human fluorinated quinolones (i.e., ciprofloxacin) continue

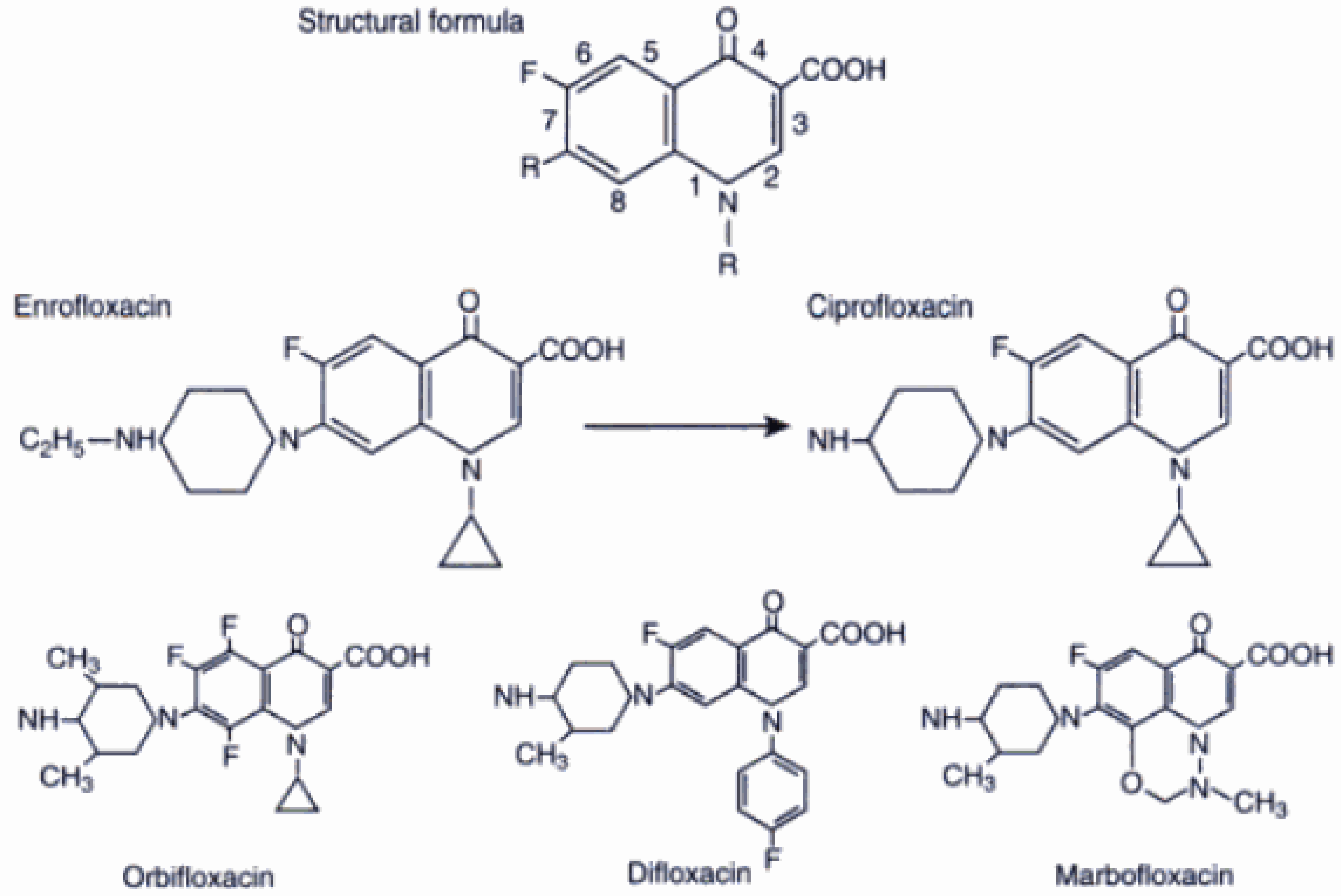

Figure 9–7. Various substitutions of the core chemical structure of the fluorinated quinolones have improved their spectrum, efficacy, and tissue penetration. The efficacy of the fluorinated quinolones depends on the ketone group at position 4 and on the carboxylic acid at position 3 (necessary for inhibition of DNA gyrase). The fluorine at position 6 markedly expanded the spectrum of nalidixic acid, the precursor of the fluorinated quinolones. Efficacy against gram-negative organisms was improved, and the spectrum was expanded against gram-positive organisms. The substitution in the 1 position differs among drugs, but those containing an ethyl group tend to be the most effective. Changes at the 5 position are responsible for many of the pharmacokinetic differences of these drugs. In addition, changes in position 8 have also proved to increase penetration of cell membranes. Changes in position 7 are pivotal in determining the ability of these drugs to inhibit DNA gyrase. Larger groups tend to be most effective. Piperazine derivatives also provide better tissue penetration as well as an increased spectrum against *Pseudomonas* sp. Enrofloxacin is converted to ciprofloxacin.

to be used in animals in the United States, although the wisdom of this use is questionable. Ciprofloxacin is the de-ethylated metabolite of enrofloxacin. Norfloxacin was the first human fluorinated quinolone used in animals in the United States; rarely is this drug used in veterinary medicine, and it is minimally addressed here.

Enrofloxacin has been available in the United States for more than 10 years, and a considerable amount of information is available for this drug. Additionally, because it is structurally similar to ciprofloxacin and because it is metabolized (approximately 20% to 25%) to ciprofloxacin, information in the human literature regarding efficacy for ciprofloxacin is largely applicable to enterofloxacin. Applying pharmacokinetic information regarding ciprofloxacin to enrofloxacin should, however, be done cautiously because differences exist among species that may affect clinical efficacy. Although marbofloxacin has been approved only a short period of time in the United States, the drug has been used since 1994 in Europe, and a considerable amount of information is available regarding this drug. In contrast, information regarding orbifloxacin and difloxacin is considerably less.

Mechanism of Action

The fluorinated quinolones impair DNA gyrase, one of several topoisomerase enzymes important to bacterial DNA replication. Bacterial DNA, which can be up to 2 m long, is normally in a supercoiled state (Neu, 1989). Replication requires uncoiling, which can cause tight kinks and breaks in the DNA. After replication, the breaks in DNA must be resealed (Fig. 9–8). Bacterial DNA gyrase, or topoisomerase II, cuts, separates, supports, and reseals the strands of DNA during replication. Although the exact mechanism of DNA damage induced by the fluorinated quinolones is not known, it is possible that "nicks" or cuts in the DNA that are not resealed lead to subsequent DNA destruction. Bacterial DNA gyrase is an ATPase-dependent enzyme comprised of two A and two B subunits. The A subunits, responsible for strand cutting and resealing (the B subunit generates energy for the process) are the target of quinolone actions.

DNA gyrase actions are inhibited at concentrations of 0.1 to 10 μg/mL. The unique mechanism of action of the fluorinated quinolones renders rapid bactericidal activity with minimal effects on the host. The rapidity of action of these drugs often is the reason for preference of these drugs compared with other equally but more slowly effective antibiotics (e.g., amoxicillin/clavulanic acid combinations for the treatment of selected pyodermas). Although mammal DNA replication is also dependent on a topoisomerase, its function is somewhat different. More importantly, affinity of host topoisomerases is less than 0.001 of that of bacterial DNA gyrase.

The concentration of fluorinated quinolones necessary to inhibit the growth of organisms (MIC) is very close to that necessary to kill the organism (MBC). The time to effect for fluorinated quinolones is very short (30 minutes); and the duration of the postantibiotic effect is up to 8 hours after drug exposure (Spoo, 1995b; Neu, 1989; Prescott, 1990; Wetzstein, 1995). The MICs of these drugs for sus-

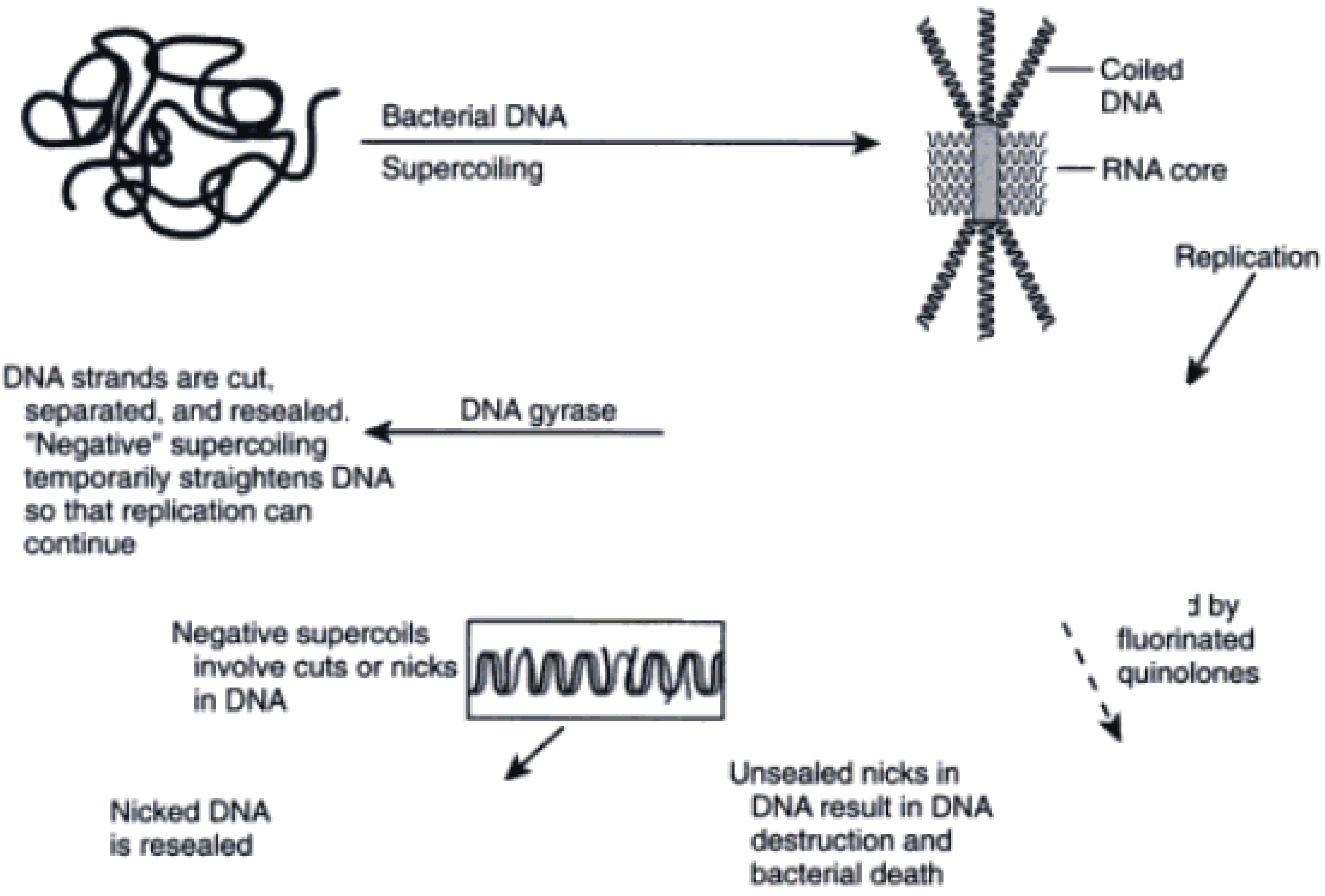
Bacterial DNA
Supercoiling
Coiled DNA
RNA core
Replication
DNA gyrase
DNA strands are cut, separated, and resealed. "Negative" supercoiling temporarily straightens DNA so that replication can continue
Negative supercoils involve cuts or nicks in DNA
Nicked DNA is resealed
d by fluorinated quinolones
Unsealed nicks in DNA result in DNA destruction and bacterial death

Figure 9–8. The mechanism of action of fluorinated quinolones. The drugs impair the α-subunit of DNA gyrase, a bacterial topoisomerase. As a result, DNA supercoiling cannot occur. DNA that has been nicked in anticipation of replication is susceptible to degradation. Bacterial DNA gyrase has a much greater affinity for the fluorinated quinolones than does mammalian DNA.

ceptible organisms are very low compared with most other antimicrobial drugs.

Spectrum of Activity

With the exception of prefloxacin, a new fluorinated quinolone, the spectra of activity of the fluorinated quinolones (see Table 9–1) are very similar among the drugs and with some notable exceptions, are similar to those of the aminoglycosides. Their spectra have been described as "broad." However, although this term might describe the class, it is only appropriate for prefloxacin. All veterinary fluorinated quinolones are characterized by a broad gram-negative spectrum. Organisms particularly susceptible include *E. coli, Klebsiella species, Enterobacter cloacae, Proteus mirabilis, Citrobacter freundii*, and *S. marcescens*. Although *P. aeruginosa* generally is included in the spectrum, efficacy against it varies with the individual drugs, with orbifloxacin reporting the highest MIC_{90} compared to peak plasma concentrations. With the exception of prefloxacin, the gram-positive spectrum of the drugs is less predictable, with selected gram-positive organisms, most notably *Staphylococcus* species and some *Corynebacterium* species being particularly susceptible. With prefloxacin, most gram-positive organisms are susceptible at low MIC. Other susceptible organisms include *Campylobacter, Salmonella, Shigella*, and *Yersinia*; the drugs exhibit variable efficacy against *Streptococcus* species and *Enterococcus faecalis* (Spoo and Riviere, 1995b; Prescott and Yielding, 1990). The MIC of most susceptible gram-negative organisms is 0.25 μg/mL or less. An exception is *P. aeruginosa*, whose MIC is often 1 to 2 μg/mL. As with aminoglycosides, anaerobic organisms are generally resistant to all fluorinated quinolones, with the exception of prefloxacin. However, enrofloxacin may achieve effective concentrations for some organisms when used at the maximum dose (20 mg/kg). Most anaerobes are included in the spectrum of prefloxacin, including *Bacteroides, Clostridium*, and *Peptostreptococcus*. The fluorinated quinolones offer several advantages compared with the aminoglycosides. They are effective against susceptible organisms located in an anaerobic environment. Other organisms that are susceptible to the fluorinated quinolones include mycoplasma, some rickettsial organisms (in vitro data and limited clinical data indicate efficacy against organisms causing ehrlichiosis and Rocky Mountain spotted fever [see Chapter 10]), and selected mycobacterial and chlamydial species. Efficacy against leptospirosis is supported by limited studies.

The efficacy of the quinolones appears to correlate more closely with peak concentrations (i.e., they are concentration-dependent) than with duration of plasma drug concentration above the MIC (Wetzstein, 1994; Walker et al., 1992); thus, care must be taken not to underdose. Duration of time that plasma drug concentrations are above the MIC may also, however, be important for selected organisms. The efficacy of the fluorinated quinolones occurs, in part, because of a long postantibiotic effect, which also is concentration dependent. Depending on the organisms, drug, and concentration, the postantibiotic effects can approximate 5 to 8 hours (Spoo and Riviere, 1995b; Power et al., 1992; Witte and Grimm, 1992).

Each of the fluorinated quinolones has been approved with a professional flexible label. For enrofloxacin and orbifloxacin, the label allows once-daily or twice-daily dosing, whereas for marbofloxacin and difloxacin, the dose is limited to once a day. The range of doses for most of the fluorinated quinolones reflects differences in susceptibility, particularly for selected gram-negative organisms, with *P. aeuruginosa* being an example of an organism whose tendency toward resistance is suggestive of the higher, once-daily dose (Marchbanks et al., 1993). Comparison of cost for these drugs should be based on the relationship of the MIC_{90} of the suspected (known) organism or the MIC of the infecting organism to the peak plasma concentration at the chosen dose. For complicated infections, comparison based on tissue concentrations may be more appropriate than that based on plasma.

It is important to note that culture and susceptibility testing does not exist for all five of the drugs. Studies in our laboratory suggest that with few exceptions, susceptibility to one drug indicates susceptibility to all drugs, including ciprofloxacin. Efficacy against *P. aeruginosa* is among the least predictable for this drug based on the efficacies of other fluorinated quinolones.

Resistance

A major advantage of the fluorinated quinolones is their lack of clinically demonstrated plasma-mediated resistance that targets DNA gyrase (topoisomerase II). Changes in the structure of this enzyme result in high resistance (up to 100-fold increase in MIC), but such resistance has been documented clinically only after point mutations. Changes in the enzyme occur in only one subunit (A) and have been documented for *E. coli, P. aeruginosa, C. freundii*, and *S. marcescens*. In contrast, plasmid-mediated resistance has been documented as a mechanism of low level resistance (8 to 10 times the resistance) for selected organisms. Resistance reflects protein-mediated efflux of the drug from the organism *(S. aureus)* or decreased drug uptake due to either a reduction in porin size *(P. aeruginosa)* or changes in the lipopolysaccharide covering of the cell wall (decreased lipid constituents thus impeding drug transport through the wall into the organism) (Spoo and Riviere, 1995b; Power et al., 1992; Witte and Grimm, 1992). Development of several of these mechanisms of resistance is inducible and may be manifested as an increase in drug MIC during therapy; discontinuation of the drug may cause the MIC to decrease.

It is important to note that development of plasmid-mediated resistance may take several decades of intense antibiotic use, suggesting that, as with other antimicrobials, the use of fluorinated quinolones ultimately will be limited by resistance. Clinically, an increasing pattern of resistance has been noted for both ciprofloxacin and enrofloxacin against several organisms, including *S. aureus, P. aeruginosa, E. coli*, and other gram-negative organisms. Prudent use of these drugs (i.e., limiting their use to critical or chronic, nonresponsive infections) may limit the development of resistance. Use of enrofloxacin should be based on culture and susceptibility data, if possible, to ensure susceptibility. The development of resistance by human bacterial organisms has led to a ban on the extralabel use of fluorinated quinolones as food additives (i.e., growth promotants).

Pharmacokinetics

The pharmacokinetics of the fluorinated quinolones are largely comparable, although individual differences may become important for some infections. After oral administration, all are generally rapidly and nearly completely (>80%) absorbed from the gastrointestinal tract. Marbofloxacin, enrofloxacin, diflotoxacin, and orbifloxacin are characterized by 100% oral bioavailability, whereas both norfloxacin and ciprofloxacin are characterized by 60% or less oral bioavailability in dogs. Magnesium and aluminum decrease oral absorption, and food may impair absorption by prolonging the rate (and thus decreasing maximum serum concentrations) but not the extent of drug absorbed. Because efficacy of these drugs is largely concentration dependent, feeding should be avoided during treatment of infections caused by intermediate-resistant microorganisms.

A parenteral preparation is available only for enrofloxacin. Although labeled for IM or SC use, the preparation can be used cautiously for IV administration. Because this class of drugs can cause mast cell degranulation and subsequent histamine release, however, enrofloxacin should be administered as a slow bolus. Some clinicians dilute the drug in saline before IV injection.

The fluorinated quinolones are well distributed to almost all body tissues, including bone, prostate, bile, and urine. Their volumes of distribution range from a low of 1.12 (marbofloxacin) to a high of 3.2 (difloxacin). Concentrations higher than plasma drug concentrations are achieved in many tissues, including urine, lung, bile, liver, kidneys, spleen, and muscle (Spoo and Riviere, 1995b; Walker et al., 1992). Therapeutic concentrations can be achieved in the prostate and CNS against many organisms. A comparison of the drugs is, however, more prudently based on tissue concentrations to MIC breakpoint or to the MIC_{90}. Among the drugs, orbifloxacin has not reported tissue concentrations. The fluorinated quinolones also are actively accumulated by white blood cells up to 140-fold compared with plasma. This has been documented for enrofloxacin and marbofloxacin.

Difloxacin is eliminated almost exclusively by hepatic metabolism to inactive metabolites. Marbofloxacin is 40% and orbifloxacin is 40% eliminated unchanged in the urine. Up to 15% of marbofloxacin is metabolized in the liver to inactive metabolites. Enrofloxacin also is eliminated predominantly in the urine as the unchanged drug, although up to 25% of the drug is metabolized to ciprofloxacin (Fig. 9–9), which subsequently is further metabolized into inactive metabolites. Therapeutic concentrations (0.2 to 1.8 μg/mL) of ciprofloxacin can be achieved for some organisms with oral therapeutic doses (5.2 to 20 mg/kg) of enrofloxacin (Walker, 1992; Boothe, 2000). It can be anticipated that enrofloxacin and ciprofloxacin will act in an additive fashion (see Fig. 9–9). The lack of metabolism for marbofloxacin or orbifloxacin may be an advantage for patients with liver disease. Additionally, each may be preferred for patients receiving other drugs metabolized by the liver because of a decreased risk of drug interactions.

Alkaline urine increases the passive reabsorption of fluorinated quinolones from the renal tubules and may prolong the elimination half-life. Difloxacin and marbofloxacin are characterized by a longer elimination half-life, which is a pharmacokinetic fact targeted by manufacturers of these drugs. The elimination half-life of antibacterial activity for enrofloxacin is prolonged by the presence of ciprofloxacin. This prolongation of efficacy may indeed be clinically relevant if efficacy of the drugs can be shown to be related to time of plasma drug concentration above the MIC. Otherwise, the advantage of a longer elimination half-life for any fluorinated quinolone is not clear. The metabolism of enrofloxacin to ciprofloxacin plus the poor oral bioavailability of ciprofloxacin and the similarities in the spectra

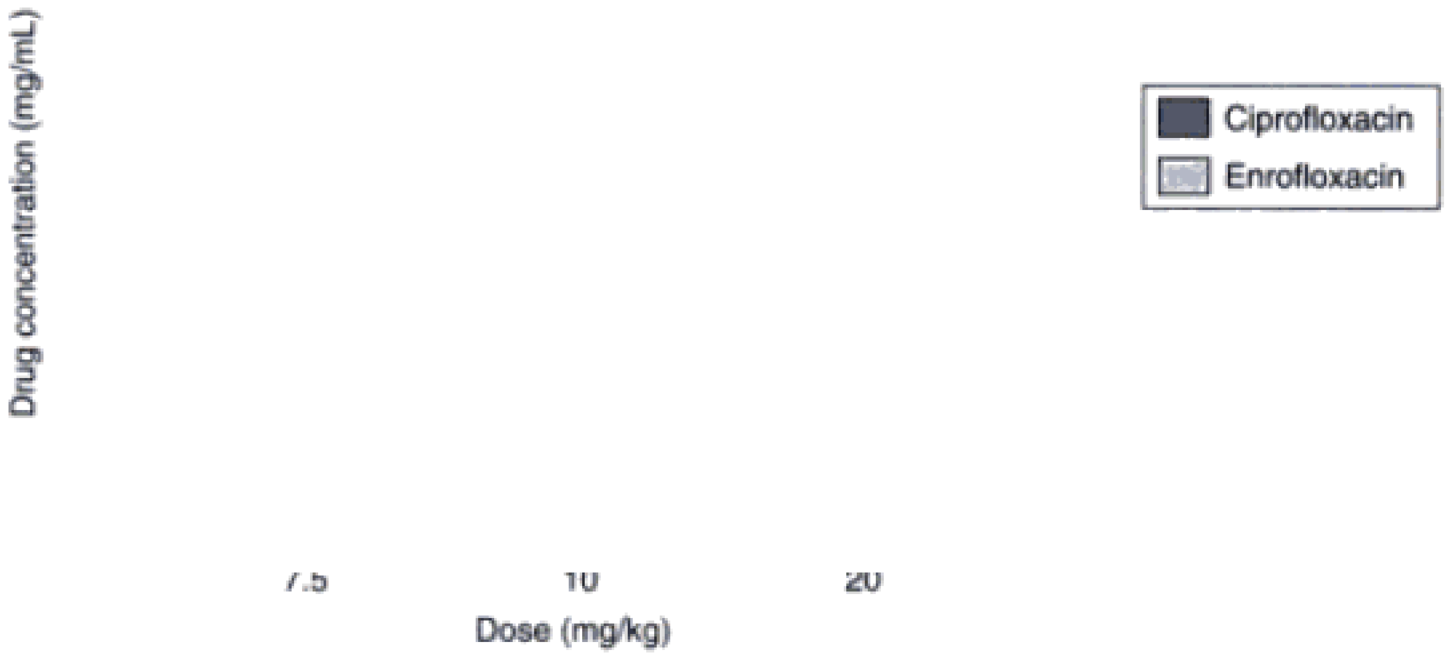

Figure 9–9. Proportion of peak plasma drug concentrations of ciprofloxacin versus enrofloxacin after administration of different doses of enrofloxacin in six dogs. Therapeutic concentrations of ciprofloxacin will be achieved in some organisms; ciprofloxacin and enrofloxacin will act in an additive fashion.

of the two drugs make use of oral ciprofloxacin in lieu of enrofloxacin for the veterinary patient a questionable choice.

Drug Interactions

The fluorinated quinolones inhibit selected drug-metabolizing enzymes and are known to prolong the elimination of selected drugs. Theophylline toxicity has been documented in humans simultaneously receiving theophylline and ciprofloxacin; a similar interaction has been reported in dogs receiving both theophylline and enrofloxacin (see Chapter 4). Because the interaction appears to involve competitive inhibition, the risk may be less for fluorinated quinolones minimally metabolized (e.g., marbofloxacin) or greatest for drugs almost completely metabolized (e.g., difloxacin). Because of chelation by magnesium, calcium, and other cations, drugs such as antacids, sucralfate, and multiple vitamins should not be administered orally at the same time as a fluorinated quinolone.

Adverse Reactions

Adverse reactions to the fluorinated quinolones are limited. Cartilage deformities and joint growth disorders have been documented in dogs after administration of any fluorinated quinolone. Lesions in adult dogs require much higher concentrations. Lesions have, however, been documented in dogs of any size at 3 to 4 months of age when administered at only five times the maximum recommended dose (marbofloxacin). Lesions occur as little as 1 to 2 days into therapy. As such, the drugs should be avoided in growing animals less than 9 (small), 12 (medium to large), or 18 (giant) months old and in pregnant animals. Lesions have also been reported in other species, including humans. The mechanism of cartilage damage may be related to chelation of magnesium in the joints. Use of chondroprotectants (i.e., polysulfated glycosaminoglycans) might be considered if fluorinated quinolone therapy must be instituted in growing dogs.

The IM administration of enrofloxacin frequently causes pain on injection. Gastrointestinal upset evidenced by vomiting, nausea, and possibly diarrhea may occur after any route of administration but particularly oral administration. Seizures have been precipitated in human and veterinary patients; predisposing factors include a pre-epileptic state, high doses, and concurrent use of nonsteroidal anti-inflammatory drugs (Halliwell et al., 1991). Adverse reactions, including nausea and vomiting, have been reported when the IM solution is given IV and may reflect histamine release. The IM solution is very alkaline (pH 10), however, and diluting the drug in saline and administering it over a 30-minute period may reduce nausea. Acute blindness (mechanism unknown) has been reported in cats receiving enrofloxacin. Blindness appears to be dose-related, being most severe at 50 mg/kg/day. Bayer Animal Health has recommended that the drug be used at doses that do not exceed 5 mg/kg/day in cats. It is not clear if other fluorinated quinolones cause the same effect. Crystalluria is a rare complication that may occur if hydration is not maintained. The role of fluorinated quinolones in acute retinal degeneration is being investigated.

Therapeutic Use

The efficacy of the fluorinated quinolones against gram-negative and, for selected drugs, some gram-positive organisms, and their excellent distribution pattern, wide therapeutic margin, and low incidence of plasmid-mediated resistance lead to their use for infections caused by susceptible organisms in any body system. Oral bioavailability allows prolonged administration on an out-patient basis, and once-daily therapy allows for convenient dosing. Resistance conferred by plasmids is limited, although it should be expected to increase. Caution should be taken with selected drugs; efficacy can vary among the drugs and among the organisms. Although one might argue that these drugs should be used to treat any infection caused by susceptible bacteria, a more prudent approach would be to reserve them for complicated or serious infections, thus minimizing the development of resistance. Intracellular accumulation of these drugs supports use for recurrent infections caused by intracellular organisms. Selected studies also support the efficacy of these drugs against rickettsial organisms and atypical mycobacteria. The unique mechanism of action of these drugs also renders them appealing for combination antimicrobial therapy.

TRIMETHOPRIM OR ORMETOPRIM/ SULFONAMIDE COMBINATIONS: INHIBITORS OF FOLIC ACID SYNTHESIS

The sulfonamides are the oldest group of antibiotics used therapeutically. Sulfonamides are derived from the first sulfonamide, sulfanilamide, itself a derivative of the azo dye Prontosil. It is perhaps the long-term use of these drugs that has led to the development of resistance that now limits their clinical use (Spoo and Riviere, 1995a).

Mechanism of Action

Folic acid is an essential substrate necessary for protein and nucleic acid metabolism. It is synthesized by bacteria in several sequential steps beginning with para-aminobenzoic acid (PABA) (Fig. 9–10). This precursor is linked to other substrates that are reduced (by dihydropteroate synthetase) to dihydrofolate. Dihydrofolate is then reduced further (by dihydrofolate reductase) to tetrahydrofolate and ultimately to folic acid. The sulfonamides are structurally similar to PABA and act as competitive substrates (antimetabolites) for the synthetase enzyme. Among the many sulfonamides used clinically are sulfadiazine; sulfamethoxazole; sulfachlorpyridazine, sulfadimethoxine, and sulfasalazine.

The sulfonamides are bacteriostatic. The diaminopyrimidines trimethoprim and ormetoprim also impair folic acid synthesis but at a different point in the metabolic pathway. They prevent the conversion of dihydrofolate to tetrahydrofolate by inhibiting the reductase enzyme. These drugs are also bacteriostatic. Combinations of a sulfonamide antimicrobial and trimethoprim inhibit bacterial folic acid synthesis at two sequential points, resulting in bactericidal effects. Mammalian cells are not affected by these drugs because they are dependent on dietary sources of folic acid—which microbes cannot use—and mammalian enzymes have a much lower affinity for the substrates than do the bacterial enzymes. Because folate metabolism is required for many cellular functions, bacterial growth is inhibited.

Spectrum of Activity

The spectrum of activity of sulfonamides is considered broad, but efficacy is variable because of the development of resistance. The spectrum of combined products includes gram-positive, gram-negative, and anaerobic organisms. The sulfonamides exhibit good efficacy against *Brucella* species, *Actinomyces, Chlamydia*, and Protozoa such as *Pneumocystis carinii* and *Cryptosporidium* species. The sulfonamides exhibit good to moderate activity against *E. coli, Enterobacter* species, *Klebsiella* species, *Proteus* species, *Pasteurella* species, and anaerobic organisms including *Actinomyces, Bacteroides, Fusobacterium*, and selected clostridia (Hirsch et al., 1979, 1985; Indiveri and Hirsch, 1986). The spectrum of these drugs does not include *Serratia, P. aeruginosa, Rickettsia*, or *Mycoplasma*. Sulfonamides alone are bacteriostatic; "potentiated sulfonamides" (i.e., combinations with trimethoprim or ormetoprim) result in bactericidal activity (Neu, 1994; Spoo and Riviere, 1995a). Potentiated sulfonamides are generally useful for uncomplicated infections of many body systems. The role of trimethoprim/sulfonamide combinations for the critically ill patient or for chronic infections should be based on culture and susceptibility information because of the incidence of resistance.

Resistance

Resistance to the sulfonamides and to trimethoprim and ormetoprim (used to treat gastrointestinal diseases) occurs

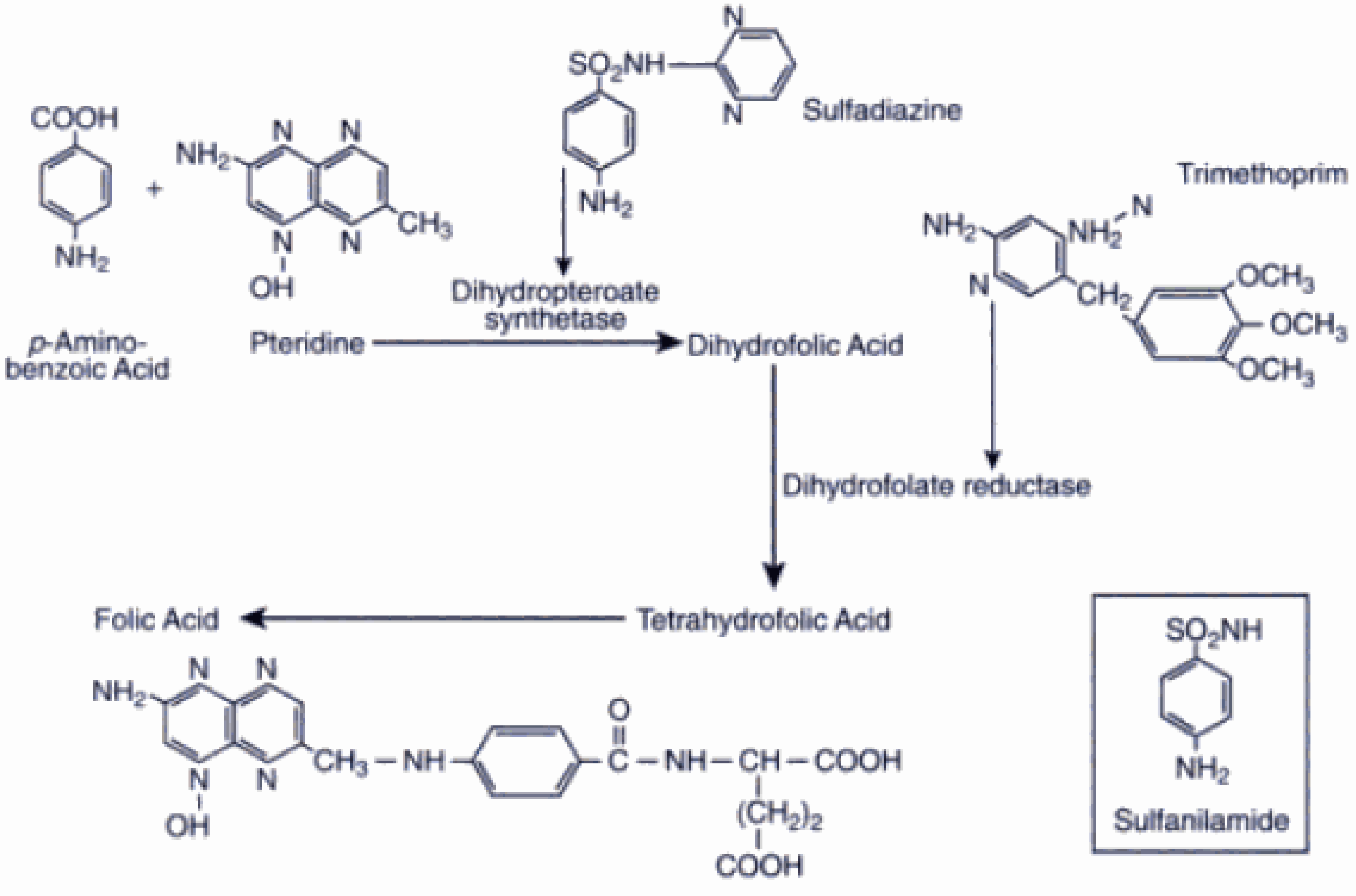

Figure 9–10. The mechanism of action of the sulfonamides and the diaminopyrimidines. By itself, either type of drug is bacteriostatic, but the two-point sequential inhibition of folic acid synthesis results in bactericidal effects. The progenitor of the sulfonamides is sulfanilamide *(inset)*.

relatively rapidly. Chromosomal resistance results in impaired drug penetration, reduced affinity of the enzyme for the substrate, or increased bacterial production of PABA. Plasmid-mediated resistance occurs rapidly due to altered drug penetration and to affinity of the enzyme for the substrate. Resistance to one sulfonamide generally results in resistance to all sulfonamides (Spoo and Riviere, 1995a). The increasing emergence of resistance has sharply limited the use of these drugs.

Pharmacokinetics

The sulfonamides are generally rapidly and completely absorbed after oral administration, although there are exceptions. Sulfasalazine is poorly absorbed as an intact molecule and is used primarily for gastrointestinal diseases. Trimethoprim and ormetoprim are also well absorbed after oral administration. Solutions intended for parenteral administration must be buffered to avoid pain and irritation due to the alkalinity of the compounds. Topical administration is not recommended because of the effects of these drugs on wound healing. An exception is made for silver sulfadiazine (Spoo and Riviere, 1995a). Protein binding of the sulfonamides varies from 15% to 99%. Sulfadiazine is 30% to 50% bound, whereas sulfasalazine is up to 99% bound.

The sulfonamides penetrate most body tissues extremely well, including the prostate. The penetration of these drugs varies with the sulfonamide component. Prostatic penetration is facilitated by a high pK_a. Sulfadiazine (pK_a 6.4) is among the best distributed sulfonamides but only achieved 11% of serum concentration in the prostate of dogs in one study. Drugs with a more basic pK_a may appear to better penetrate the prostate, although this may reflect ion trapping in prostatic fluids. Trimethoprim achieves tissue concentrations that are four times higher than those in plasma. Sulfadiazine can attain therapeutic concentrations in CSF, particularly if given IV, and is the preferred sulfonamide for CNS infections (Spoo and Riviere, 1995a). The combination of a sulfonamide with a diaminopyramidine at a ratio of 1:5 trimethoprim/sulfonamide (total dose 30 mg/kg divided into twice daily doses) results in a bactericidal effect and a tissue distribution ratio of 1:20 in most tissues (Neu, 1994).

The sulfonamides are eliminated primarily by acetylation in the liver. Dogs are characterized by weaker acetylation than most other species, and metabolism occurs via other pathways. Acetylated metabolites of sulfonamides are often less soluble than the parent compounds, which increases the risk of renal damage should drug precipitate and form crystals. Drugs are renally excreted as either the parent compound or the conjugated metabolite by either glomerular filtration or active tubular secretion. Both passive reabsorption and enterohepatic circulation can prolong the elimination half-life of selected sulfonamides (Spoo and Riviere, 1995a). The elimination half-lives of the drugs vary with the sulfonamide component and among the species. The duration at which sulfonamides remain in the body leads to classification as short acting (12 hours or less: sulfacetamide, sulfathiazole, and sulfisoxazole), intermediate acting (12 to 24 hours: sulfadimethoxine, sulfisoxazole, sulfamethoxazole, sulfapyridine, sulfamethazine, and sulfadiazine), and long-acting (longer than 24 hours) (Spoo and Riviere, 1995a).

After oral administration, sulfasalazine is partially absorbed in the small intestine. It undergoes enterohepatic circulation and ultimately is eliminated in the urine. Most of the drug (70%) is metabolized by colonic bacteria to its component parts: sulfapyridine and 5-aminosalicylic acid. Sulfapyridine is rapidly absorbed and subsequently eliminated in urine. The 5-aminosalicylic acid may provide the major therapeutic benefit for chronic inflammatory bowel disease (Spoo and Riviere, 1995a).

Adverse Effects

Although the sulfonamides are generally safe drugs, the advent of hypersensitivity drug reactions (immunologic) has limited their use. Immune-mediated diseases of the skin, kidney, liver, and eye are not dose dependent and occur in response to any of the sulfonamides. Keratoconjunctivitis sicca has been reported in dogs after treatment with sulfasalazine, sulfadiazine, and sulfamethoxazole. Toxicity is thought to target the lacrimal gland. Prognosis is variable, and normal function may not recur once the drug is discontinued. Prognosis is more favorable for younger dogs receiving the drug for a short period of time.

Sulfonamides at high doses (30 mg/kg twice daily) can profoundly alter thyroid physiology, causing decreased iodinization of colloid and decreased concentrations of thyroxin and thyronine (Hall, 1993). Decreases are clinically relevant by 3 weeks of therapy and will return to normal within 3 weeks after therapy is discontinued. Aplastic anemia and thrombocytopenia have been reported after therapy with sulfonamides, although their cause is not clear. Impaired folic acid synthesis has been reported as a cause, but direct bone marrow suppression should also be considered. Sulfonamides, and sulfadiazine in particular, appear to be safe at doses higher than those used therapeutically. For example, dogs show no adverse effects (other than antithyroid effects as discussed above) when treated with sulfadiazine at 300 mg/kg a day for 20 days. Cats appear to be more sensitive to the effects of trimethoprim/sulfonamide combinations. Doses of 300 mg/kg per day for 10 to 30 days orally in cats resulted in lethargy, anorexia, anemia, leukopenia and increased blood urea nitrogen. Mammalian cells can use dietary folic acid, and supplementation might be considered for patients that develop anemia (Spoo and Riviere, 1995a). Before the advent of triple and potentiated sulfonamide preparations, crystalluria was a common side effect, with subsequent renal damage. At high doses of any sulfonamide product, it is recommended that the hydration status of the animal be ensured to be normal.

Therapeutic Use

Because of the advent of resistance, the use of sulfonamides is limited to uncomplicated infections of most body systems. The concentration in urine supports the use of potentiated sulfonamides for urinary tract infections. Trimethoprim/sulfonamide combinations are indicated for treatment of infections caused by susceptible bacteria in difficult to penetrate tissues such as the prostate and CNS (Spoo and Riviere, 1995a). These drugs are among the drugs of choice for treating *Nocardia* and *Actinomyces*.

TETRACYCLINES AND CHLORAMPHENICOL

Because their mechanisms of action and spectra of activity are similar, tetracyclines and chloramphenicol are discussed together (see Fig. 9–4). Both drugs have been widely used in the past, but the development of resistance and human toxicity to chloramphenicol have severely curtailed their use.

Mechanism of Action

Both tetracyclines and chloramphenicol bind bacterial ribosomes and impair protein synthesis (see Fig. 9–5). As a result, both are bacteriostatic in action and should not be used for the immunocompromised patient, whether the condition is disease or drug induced (i.e., glucocorticoids or anticancer drugs). The tetracyclines bind to 30S ribosomal subunits. Because tRNA binding is prevented, amino acids cannot be added to the peptide chain and protein synthesis is impaired. Chloramphenicol binds to the 50S subunit of bacterial ribosomes and also impairs protein synthesis. Although host ribosomes do not bind as effectively as do bacterial ribosomes to each drug, some host ribosomal activity will be impaired.

Spectrum of Activity

The tetracyclines and chloramphenicol are considered broad spectrum (see Table 9–2), being effective against gram-positive, gram-negative, and anaerobic organisms. *P. aeruginosa* is generally not included. The spectrum of action also includes *Chlamydia, Mycoplasma, Rickettsia*, and *Hemobartonella* organisms. As general rule, tetracyclines are considered more effective than chloramphenicol for the latter organisms, but chloramphenicol tends to be more clinically effective for other organisms.

Resistance

Most resistance to tetracyclines results from transport of the drug out of the microbial cell. Resistance to chloramphenicol is caused by destruction (acetylation) of the drug by microbial enzymes.

Pharmacokinetics

The oral absorption of tetracyclines is variable, with chlortetracycline being the least bioavailable, oxytetracycline more so, and doxycycline, the most lipid soluble of the tetracyclines, being 100% bioavailable. Absorption is decreased in the presence of divalent and trivalent cations such as those present in milk products or antacids. Tetracyclines, particularly doxycycline, are widely distributed to most body tissues. Doxycycline is able to penetrate cell membranes and thus access intracellular organisms. Doxycycline is 99% protein bound, which prolongs its elimination half-life. Tetracyclines, with the exception of lipophilic tetracyclines such as minocycline and doxycycline, do not penetrate the CSF. The latter drugs are thus preferred because of better tissue penetrability for treatment of infections caused by susceptible bacteria in "difficult to penetrate" tissues. Minocycline is characterized by a larger volume of distribution in people than is doxycycline, suggesting better tissue penetrability. Tetracyclines are incorporated into forming bone and the enamel and dentine of unerupted teeth and cause bone discoloration of teeth upon eruption.

With the exception of doxycycline and minocycline, the tetracyclines are eliminated by both renal (approximately 60%) and biliary (40%) excretion. Presumably, minocycline is eliminated essentially in the bile, whereas the route of elimination of doxycycline is less obvious. In humans, it is eliminated by both renal (41%) and biliary (59%) mechanisms. In dogs, bile may be the predominant route. Tetracyclines undergo enterohepatic circulation. Toxic concentrations may accumulate in patients with renal disease. Differences that justify use of minocycline instead of doxycycline are difficult to ascertain. Adverse reactions to minocycline may, however, be more likely.

Chloramphenicol is very well absorbed after oral administration. The liquid form is less well absorbed. The palmitate form should not be used for cats because of variability in oral absorption. The succinate form is well absorbed after IM administration. It is hydrolyzed in plasma to its free base. Chloramphenicol is one of the more lipid soluble of the clinically used drugs and achieves high concentrations in most body tissues, including the CSF. It is, however, unlikely to achieve bactericidal concentrations in most tissues, including the CNS. Most of the drug is eliminated by hepatic metabolism. Glucuronidation is a major route of elimination of chloramphenicol. Cats eliminate chloramphenicol more slowly due to deficiencies in both phase I and phase II metabolism. Greater concentrations may occur in cat urine than in dog urine as a result (Spoo and Riviere, 1995b). Pediatric patients also may not eliminate chloramphenicol as efficiently as young adult dogs.

Both chloramphenicol and the tetracyclines are available as IV, parenteral, and ocular preparations.

Adverse Effects

Tetracyclines cause several adverse effects in small animals. Toxicity may be worsened in patients with renal disease due to decreased elimination. Gastrointestinal upset follows direct irritation of the gastrointestinal mucosa after oral administration. Rarely, hepatotoxicity may occur. Rapid IV administration may result in collapse. Although the mechanism is not certain, calcium binding may be important. Intravenous administration of tetracycline has caused anaphylactic shock in dogs. Hypersensitivity has also been reported in a dog after IM administration of tetracycline. Minocycline may be more likely to cause allergic drug reactions. Lesions characterized by erythema of the skin and mucous membranes occurred in dogs after administration of most doses of minocycline. Anemia may also occur (10 mg/kg IV). Brown discoloration of teeth may occur due to chelation of tetracyclines in calcium deposits of dentin and, to a lesser degree, enamel. The drug must be administered during tooth development (i.e., prenatally or within 1 month after birth). Other side effects caused by tetracyclines include drug fever (in cats), an antianabolic effect, and a Fanconi-like syndrome in the kidneys (Spoo and Riviere, 1995b).

A major toxic concern with chloramphenicol for humans is that both reversible dose-dependent and irreversible dose-independent (rare) bone marrow depression may occur. Bone marrow depression can also occur in animals. Dose-dependent bone marrow depression may occur due to suppression of bone marrow precursor cells after mitochondrial damage. Irreversible bone marrow suppression may reflect reduction of the NO_2 group to a toxic metabolite that causes stem cell damage. Although cats appear more sensitive to chloramphenicol-induced toxicity than dogs, toxicosis appears rapidly reversible once the drug is discontinued. Toxicity occurs in cats after 7 days of therapy at 50 mg/kg IM. The drug can, however, be used for 7 to 10 days safely in cats after oral administration of the crystalline form (capsules) at the rate of 50 mg/cat (Spoo and Riviere, 1995b). The antianabolic effects of chloramphenicol may result in impaired protein synthesis in the patient; however, despite earlier concerns, impaired immune response to vaccines does not appear to occur. Chloramphenicol is a potent inhibitor of drug metabolizing enzymes and inhibits the hepatic metabolism of other drugs, potentially causing toxicity should drug concentrations increase. Phenobarbital toxicity has occurred in as few as 3 days of chloramphenicol therapy. Prolonged sleeping times have been documented after administration of pentobarbital to animals also receiving phenobarbital (Spoo and Riviere, 1995b).

LINCOSAMIDES: LINCOMYCIN AND CLINDAMYCIN

The lincosamides include lincomycin and clindamycin (see Fig. 9–4). Like chloramphenicol, clindamycin is an inhibitor of the 50S subunit of the bacterial ribosomes (see Fig. 9–5). It is effective against aerobic gram-positive cocci and anaerobic organisms (Braden et al., 1988). Clindamycin is generally bacteriostatic but can be bactericidal at concentrations that can be achieved in some tissues. Clindamycin is only available in oral preparations in veterinary medicine, although an injectable product is available in human medicine. Distribution to most body tissues, including skin and bones, is excellent (Weber et al., 1980). Clindamycin actively accumulates in white blood cells and may achieve bactericidal concentrations at some sites. It is eliminated as either the parent drug or its metabolites in the bile. Resistance by *Staphylococcus* species and *Bacteroides* species appears to be limiting the efficacy of clindamycin. Pseudomembranous colitis is a reported side effect in humans due to overgrowth of *Clostridium difficile*. Because of similar mechanisms of action, this drug should not be combined with chloramphenicol or erythromycin. It has been combined with aminoglycoside treatment of polymicrobial infections involving gram-negative and anaerobic organisms. Clindamycin has been cited for its efficacy in the treatment of chronic gingivitis or peridontal disease. Unlike many other drugs with a favorable spectrum, it is able to penetrate the biofilm that protects the causative organisms. Because of its anaerobic and gram-positive spectrum, clindamycin often is chosen as one component of combination antimicrobial therapy.

MACROLIDES

Erythromycin (see Fig. 9–4) and azithromycin are macrolide antibiotics used in veterinary medicine. Macrolides are inhibitors of ribosomes; they bind to the 50S subunit (see Fig. 9–5), causing bacteriostatic effects. The drugs are very lipid soluble and are accumulated in white blood cells, prolonging efficacy. Both are available as oral preparations. The spectrum of activity of erythromycin includes gram-positive organisms and anaerobes (hence it is often used as a "penicillin substitute" by people allergic to penicillin); that of azithromycin includes *Corynebacterium* and *Pasteurella* species.

Erythromycin has been used effectively for the treatment of dermatitis caused by *Staphylococcus intermedius* in dogs and other selected gram-positive infections. Side effects of erythromycin are primarily gastrointestinal; up to 50% of patients may show signs of gastrointestinal upset. This may be related, in part, to the prokinetic effects of erythromycin on the gastrointestinal tract. Azithromycin is a macrolide recently approved for use in humans. Compared to erythromycin, it is effective against more gram-negative organisms and is accumulated 200-fold (compared with plasma) in several tissues, including the respiratory tract. Accumulation in tissues in cats has led to its use at 5 mg/kg once a week for prevention of *Mycoplasma* infection in catteries.

VANCOMYCIN

Vancomycin has had an important role in the treatment of human patients infected with penicillin-resistant staphylococci, but the advent of penicillinase-resistant β-lactams and the incidence of adverse reactions have curtailed its use. Vancomycin is a large glycopeptide with three components each of which may be responsible for its antimicrobial action on bacterial cell walls (Ingerman and Santoro, 1989). Vancomycin binds to the free end of the pentapeptide, sterically interfering with its elongation. Resistance has been impeded by the high specificity of the drug; multiple mutations would be required to change the enzymes currently targeted by vancomycin. Resistance that has developed by *E. faecalis* resulted from synthesis of a new protein that interferes with vancomycin. Its spectrum of activity is limited to *Staphylococcus* and *Streptococcus* species. Selected *Enterococcus, Clostridium*, and *Corynebacterium* species are also generally susceptible.

With the exception of enterococcal organisms, the effects of vancomycin are generally bactericidal. Administration is limited to the IV route except for treatment of pseudomembranous colitis caused by *C. difficile*. Vancomycin is distributed to most body tissues except the CNS. It is renally eliminated; drug concentrations may become toxic if doses are not modified for the patient with renal disease. Hypersensitivity in human patients warrants slow (60-minute) IV infusion of drug diluted in fluid. Its use for veterinary patients should be limited to treatment of organisms resistant to other drugs as based on culture and susceptibility data.

RIFAMPIN

Rifampin is a large complex antimicrobial derived from rifamycin B produced by *Nocardia mediterria* (Spoo and Riviere, 1995a). It is an inhibitor of the B subunit of DNA-dependent RNA polymerase and thus suppresses RNA synthesis. Mammalian RNA polymerase requires much higher concentrations than microbial before it is inhibited. Rifampin can achieve bactericidal concentrations in some tissues, but very rapid development of resistance severely curtails its use. Its spectrum of activity includes gram-positive (especially *Staphylococcus* species) organisms. It is also effective against *Mycobacterium, Neisseria*, and *Chlamydia* species and has been used to treat *Clostridium* and *Bacteroides* species. Rifampin has limited activity against gram-negative organisms (including *Brucella*). Resistant gram-negative organisms include *E. coli, Enterobacter* species, *K. pneumoniae, Proteus* species, *Salmonella* species, and *P. aeruginosa*.

Differences in the MICs between gram-positive (generally 0.1 μg/mL) versus gram-negative (generally 8 to 32 μg/mL) organisms reflect differences in ability to penetrate gram-negative organisms. Highly susceptible gram-positive organisms are considered to have an MIC of 0.25 μg/mL or less. The MICs of gram-negative organisms range from less than 0.008 to more than 16 μg/mL; resistant gram-negative organisms are considered to have an MIC greater than 4 μg/mL. Resistance to rifampin develops quickly when used as the sole antibiotic. A single mutation changes the affinity of the target enzyme for the drug. Resistance can be decreased with combination therapy with erythromycin, most β-lactam antibiotics, and selected aminoglycosides. Rifampin has shown some efficacy against fungal microorganisms (*Histoplasma capsulatum, Aspergillus* species, and *Blastomyces dermatitidis*) when combined with amphotericin B. Amphotericin B apparently facilitates movement of rifampin through the fungal cell wall into the organism where RNA polymerase then can be accessed.

Rifampin is very lipid soluble, distributing well to most body tissues. It concentrates in white blood cells (Spoo and Riviere, 1995a). Rifampin is rapidly eliminated after acetylation to an active metabolite in the bile and undergoes enterohepatic circulation. It is a potent inducer of microsomal enzymes and as such will shorten the elimination half-life of a number of drugs. Plasma drug concentrations of rifampin decrease after multiple dosing because of induction. The major therapeutic indication for rifampin is in combination with erythromycin for the treatment of foal pneumonia caused by *Rhodacoccus equi*. In humans, however, the drug is effective against *Mycobacterium* species. The drug is generally well tolerated, although hepatopathy (manifested as jaundice) has been reported in human patients with liver disease who receive rifampin. The drug causes an orange-red discoloration of urine that can stain hair and fabrics.

MISCELLANEOUS ANTIBIOTICS

Bacitracin

Bacitracin is a complex polypeptide isolated from *Bacillus subtilis*. It inhibits peptidoglycan synthesis in bacteria by interfering with the enzyme responsible for movement of cell components through the membrane. Its spectrum of activity includes gram-positive and very few gram-negative organisms. Systemic use causes nephrotoxicity, and use is limited to topical administration. The drug is not absorbed after oral administration and can be used to treat gastrointestinal infections caused by susceptible organisms (Spoo and Riviere, 1995a; Neu, 1994).

Novobiocin

Novobiocin is derived from coumarin and is effective against both gram-positive and gram-negative organisms. The drug is particularly efficacious against *Staphylococcus* species. Its mechanism of action is not certain but involves both cell membrane and cell wall synthesis. Novobiocin causes a number of toxic effects when used systemically, including bone marrow suppression, nausea, vomiting, and diarrhea. Its use is limited to topical application (Spoo and Riviere, 1995a; Neu, 1994).

Polymyxins

Polymyxins are a group of large acetylated decapeptides produced by a *Bacillus* species. At least six compounds have been identified, of which only two, polymyxin and colistin, are used clinically. Polymyxins are cationic detergents that interact and interfere with the phospholipid of the bacterial cell membrane, resulting in increased permeability. The polymyxins are thus bactericidal. However, a number of compounds can interfere with their activity, including divalent cations, purulent exudate, fatty acids, and quaternary ammonium compounds. The spectrum of activity of the polymyxins includes most gram-negative organisms, including *P. aeruginosa*. Two exceptions include *Proteus* species and most *Serratia* species. The drugs are weak bases (pK_a 8 to 9) and are not orally bioavailable. As such, they have been used to "sterilize" the gastrointestinal tract.

Elimination is principally via the kidneys, which is also the primary site of toxicity. Glomerular and tubular epithelial damage have limited their usefulness. Other side effects include respiratory paralysis (after rapid IV administration), CNS dysfunction, fever, and anorexia. Use of the polymyxins is primarily limited to topical administration. Eventually, polymyxin (or a related compound) may prove therapeutically useful for treatment of endotoxic shock primarily because of its effects on endotoxin. Polymyxin protects against gram-negative endotoxemia by binding to the anionic lipid component of the lipopolysaccharide at concentrations much lower than those associated with toxicity.

Nitrofurans

The nitrofurans are synthetic compounds whose antimicrobial activity occurs through the 5-nitrofuran group (Spoo and Riviere, 1995a; Neu, 1994). Nitrofurantoin and furazolidone are examples. These drugs block oxidative reactions necessary for formation of acetyl coenzyme A. The drugs are bacteriostatic. Their spectrum of activity is principally against gram-negative organisms but also includes some gram-positive organisms and some protozoa. Nitrofurans are orally bioavailable but require an acidic environment to cross cell membranes. Fifty percent of nitrofurantoin is eliminated in urine in an active form, thus making the drug amenable for treatment of urinary tract infections. Its use is, however, limited by gastrointestinal and systemic toxicity. In addition, the drug is very expensive. Its use is limited to infections of the urinary tract that are not susceptible to other drugs.

Methenamine

Methenamine is a chemical that releases formaldehyde and ammonia upon hydrolysis. The degree of hydrolysis, and thus antibacterial efficacy, is pH dependent. The drug is bactericidal in an acid environment and bacteriostatic in a more alkaline environment. As such, it is less effective in the presence of urease-producing bacteria that alkalinize the urine. Its spectrum of activity includes both gram-positive and gram-negative organisms. Methenamine is orally bioavailable and reaches high concentrations in urine (Spoo and Riviere, 1995a). The chemical is used primarily to treat urinary tract infections in dogs. Generally, it is used in combination with urinary acidifiers to enhance antibacterial actions.

Metronidazole

Metronidazole impairs microbial RNA and DNA synthesis but only after it has undergone (nitrous) reduction in the organism. Thus, its efficacy depends on a low redox potential such as can be achieved only in an anaerobic environment (Muller, 1983). It is rapidly bactericidal against all gram-negative (e.g., *B. fragilis*) and most gram-positive (e.g., *Clostridium* species) anaerobic bacilli. Metronidazole is well distributed to all body tissues and can penetrate the blood-brain barrier. Elimination occurs primarily by hepatic metabolism. Adverse effects include seizures (Fitch et al., 1991; Neff-Davis et al., 1981) and gastrointestinal upset.

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Treatment of Bacterial Infections

10

Dawn Merton Boothe

- INTRODUCTION
- INFECTIONS OF THE CENTRAL NERVOUS SYSTEM
- Meningitis
  - Physiology and Pathophysiology
  - Antimicrobial Selection
  - Adjuvant Therapy
  - Adverse Reactions
- Otitis Media
- Otitis Interna
- INFECTIONS OF THE MUSCULOSKELETAL SYSTEM
- Osteomyelitis
  - Pathophysiology
  - Therapy
- Septic Arthritis
  - Pathophysiology
  - Therapy
- RESPIRATORY TRACT INFECTIONS
- Pathophysiology
  - Bacterial Tracheobronchitis
  - Bacterial Pneumonia
  - Pyothorax
- URINARY TRACT INFECTIONS
- Pathophysiology
- Therapy
  - Sequelae of Drug Therapy
  - Identification of the Target
  - Antimicrobial Selection
  - Empirical Therapy
  - Duration of Therapy
  - Prophylaxis
  - Adjuvant Therapy
- Pyelonephritis
- Prostatitis
  - Pathophysiology
  - Antimicrobial Selection and Use
- INFECTIONS OF THE UTERUS
- Endometritis
- Pyometra
- DERMATOLOGIC INFECTIONS
- Pyoderma
  - Microbial Flora
  - Predisposing Factors
  - Pathophysiology
  - Considerations in Drug Selection
  - Antimicrobial Selection
  - Duration of Therapy
  - Adjuvant Therapy
- Miscellaneous Infections
- OTITIS EXTERNA
- Pathophysiology
- Antimicrobial and Adjuvant Options
- Treatment of Specific Causes of Otitis Externa
  - Chronic Otitis
  - Acute Otitis Externa
  - Bacterial Otitis
  - *Malassezia pachydermatis*
- INFECTIONS OF THE GASTROINTESTINAL TRACT
- Oral Cavity
- Esophagus Through Small Intestine
  - Megaesophagus
  - Stomach
- Small and Large Intestines
  - Normal Control Mechanisms
  - Factors Facilitating Infection
  - Treatment of Bacterial Diarrhea
  - Adjuvant Therapy
- INFECTIONS ASSOCIATED WITH BACTEREMIA
- Infective Bacterial Endocarditis
  - Pathophysiology
  - Antimicrobial Therapy
- Peritonitis and Other Intra-abdominal Infections
  - Pathophysiology
  - Antimicrobial and Adjuvant Therapy
- Sepsis and Septic Shock Syndrome
  - Definitions
  - Pathophysiology
  - Antibacterial Therapy
  - Adjuvant Therapy
- MISCELLANEOUS INFECTIONS
- L-Form Bacterial Infection
- Brucellosis
  - Pathogenesis
  - Antimicrobial and Adjuvant Therapy
- Leptospirosis
  - Pathogenesis
  - Antimicrobial Therapy
- Lyme Borreliosis
- Higher Bacteria: Nocardiosis and Actinomycosis
  - Pathogenesis
  - Antimicrobial and Adjuvant Therapy
- Mycobacteria
  - Tuberculosis
  - Leprosy
  - Atypical Mycobacteria
  - Melioidosis and Tularemia
- RICKETTSIAL DISEASES
- Ehrlichiosis
  - Causative Organisms
  - Pathophysiology
  - Antimicrobial and Supportive Therapy
- Rocky Mountain Spotted Fever
  - Causative Organism
  - Pathophysiology
  - Antimicrobial and Supportive Therapy
- Other Rickettsial Diseases
- ANAEROBIC INFECTIONS
- Pathogenesis
- Factors Impacting Selection of Antimicrobials
- Antimicrobial Drugs
  - β-Lactam Antibiotics
  - Other Antimicrobials
  - Selected Anaerobic Infections
- ANTIMICROBIAL PROPHYLAXIS
- SURGICAL PROPHYLAXIS
- Type of Surgery
- Potential Pathogens Encountered
- Host Competence
- Pharmacologic and Antibacterial Properties

INTRODUCTION

This chapter focuses on the treatment of bacterial infections on a systems basis. In addition, selected organisms are discussed because of their unique nature and the difficulties encountered when treating infection. Because of limited information in veterinary medicine, information is largely drawn from human medicine.

INFECTIONS OF THE CENTRAL NERVOUS SYSTEM

Meningitis

Meningitis serves here as the prototypic infection of the central nervous system (CNS).

Physiology and Pathophysiology

Most infections reach the CNS via a hematogenous route. Infections of the CNS are problematic for three reasons unique to the CNS: Its cellular component reflects functional specialization, it is sequestered from the rest of the body by physiologic barriers, and it is closely confined within rigid skeletal structures (Greenlee, 1995). The cellular specialization is of diagnostic benefit in the identification and localization of infections of the CNS because clinical signs are often referred to a specific region of the brain. The course of CNS infection is impacted by the relationship of the brain and spinal cord to the vasculature, meninges, and skeletal structure. The brain is suspended in cerebrospinal fluid (CSF) and is surrounded by the meninges (pia mater and arachnoid [the leptomeninges], and the dura mater). Infections of the leptomeninges tend to involve their entire surface surrounding the brain and spinal cord. In contrast, infections of the dura mater tend to be limited and sharply circumscribed. With persistent infection of the meninges, increased intracranial pressure results from extensive cerebral edema and hydrocephalus. Infections of the meninges of the spinal cord are less limited and often extend longitudinally the length of the cord (Greenlee, 1995).

About 85% of CSF is produced by the choroid plexus of the lateral, third, and fourth ventricles. The CSF flows into the subarachnoid space, circulates around the brain and spinal cord by bulk flow, and is reabsorbed through the arachnoid. The CSF is totally recirculated in 3 to 4 hours. The choroid plexus is physiologically similar to renal tubules, even containing similar secretory mechanisms. Indeed, specialized transport systems allow the movement of organic acids (including many β-lactams) against a concentration gradient out of the CSF. In cases of infections involving the ventricles, because of the flow pattern of CSF, intrathecal administration of drugs does not result in predictable drug concentrations in the ventricles. Rather, drug must be directly instilled into the ventricles. Infections of the CNS can impair CSF reabsorption across the arachnoid villi, resulting in hydrocephalus (Greenlee, 1995).

Capillaries of the brain and cord (with the exception of the choroid plexus) differ from other capillaries. First, the vascular endothelium is characterized by tight junctions rather than intracellular clefts. Second, they are surrounded by the foot processes of astrocytes. Both form a barrier to passive diffusion of drugs and their compounds. Only compounds that are actively transported or are of sufficient lipid solubility can pass out of the capillaries into the brain. The barrier impacts the movement of antibiotics. In addition, impaired movement of immunoglobulins, complement, and other mediators of the immune response impacts antimicrobial selection in that bacteriostatic drugs are much less desirable (Greenlee, 1995; Tunkel and Scheld, 1995).

Vascular damage during the course of infection can impact the course of infection. Hypertrophy of the endothelium (as might occur with persistent bacterial infection) or infection of the endothelial cells (as occurs with Rocky Mountain spotted fever or others) can cause thrombosis or embolization to arteries or veins. Loss of capillary integrity contributes to cerebral edema and movement of microorganisms into the brain. At the same time, capillary permeability facilitates movement of antibiotics that normally cannot cross the cerebral or meningeal capillaries into the site of infection (Greenlee, 1995; Tunkel and Scheld, 1995).

The inflammatory response of the CNS also differs from that in other body tissues. The response tends to be less intense and is characterized by infiltration by microglial cells and proliferation of astrocytes. Abscessation is slower and, rather than fibrosis, involves gliosis. Host response to infection in the CNS involves antibody, cell-mediated immunity, and complement. Normally excluded from the CNS, the presence of antibody indicates damage to the blood-brain barrier or synthesis of immunoglobulin from cells that have been able to penetrate the brain parenchyma. Antibody protection is important to bacterial meningeal infections and may determine the outcome. Cell-mediated immunity, on the other hand, is the predominant host response to fungal or intracellular parasites. Infections by selected organisms, such as *Mycoplasma,* may lead to a host response to both the infecting organism and host proteins (e.g., myelin). Despite the role of the immune system in bacterial infections of the CNS, host defenses remain inadequate for control of the infection. Indeed, the relative lack of opsonization, complement, and immunoglobulins may allow bacterial survival in the subarachnoid space (Greenlee, 1995; Tunkel and Scheld, 1995).

Bacterial products can contribute to the development of cerebral edema. Release of cytokines and tumor necrosis factor is mediated by materials such as endotoxin of gram-negative organisms and teichoic acid produced by *Staphylococcus aureus.* Whereas changes in capillary permeability may increase antibiotic movement across the blood-brain barrier, antibiotic therapy may actually initially worsen cerebral edema, as bacterial death causes release of more mediators of inflammation. Inflammation, hemorrhage, hydrocephalus, and edema may cause displacement of the brain or spinal cord. Herniation may be a life-threatening sequelae (Greenlee, 1995). The potential release of endotoxin may be an important consideration in the initial selection of an antimicrobial; drugs that minimize endotoxin release yet still penetrate the blood-brain barrier include imipenem and the fluorinated quinolones.

Antimicrobial therapy is likely to be impacted by the presence of purulent material. As in all body systems, the microenvironment can negatively impact antibacterial therapy. In the presence of meningitis, lactate accumulates in the CSF, causing the pH to decrease. Antibacterial activity of weakly basic antibiotics may decrease, particularly for the aminoglycosides and potentially for the fluorinated quinolones (Tunkel and Scheld, 1995).

Antimicrobial Selection

Successful antimicrobial therapy of CNS infections is facilitated by use of a bactericidal drug and maximization of plasma drug concentrations such that bactericidal concentrations are achieved in the CNS. The CNS is relatively immunoincompetent, thus increasing the concentration of drug necessary for effective therapy. Studies in animal models have shown that the rapid bactericidal killing in the CSF requires drug concentrations that exceed the minimum bactericidal concentration (not minimum inhibitory concentration [MIC]) by 10- to 20-fold (Tunkel and Scheld, 1995). Drugs that can be given intravenously are preferred to oral preparations; intramuscularly and subcutaneously are second choice preferences to oral administration. Doses should be maximized because of poor penetrability of the blood-brain barrier.

Antibiotics to treat the CNS are often selected empirically because of difficulties encountered when collecting culture and susceptibility data. Organisms most likely infecting the CNS are delineated in Table 8–3. After identifying the most likely infecting organism and drugs effective against the organism (Chapters 8 and 9), antibiotics should be selected next based on movement into the CNS. Drug penetration of the blood-brain barrier is particularly challenging because the barrier not only prevents movement of antimicrobials into the CNS but also actively transports out or destroys some antimicrobials (i.e., selected β-lactams). Drugs that are more likely to penetrate the barrier are characterized by high lipid solubility, small molecular weight, and low protein binding (Tunkel and Scheld, 1995). Drug movement into the CNS is summarized in Table 8–8. In general, imipenem, trimethoprim/sulfonamide, fluorinated quinolones, rifampin, and metronidazole can achieve bactericidal concentrations for some infections in the CNS; chloramphenicol and doxycycline or minocycline achieve bacteriostatic concentrations (LeFrock et al., 1984). Drugs that should be avoided or whose doses should be further increased (Table 10–1) for treatment of CNS infections because of poor penetration include the aminoglycosides; many β-lactams, including carbenicillin, cephalothin, cefazolin, cefotetan; and clindamycin, erythromycin, and tetracycline. Drugs recommended for treatment of meningitis in humans are listed in Table 10–1. Inflammation will increase movement of several antibiotics, including many β-lactams and vancomycin. It is important to remember, however, that transport mechanisms exist to move many drugs (particularly β-lactams) out of the CNS. In addition, as inflammation resolves, permeability of the barrier may also resolve, thus once again precluding antibiotic distribution to the site of infection. Maximal doses of antibiotics (increasing by 50% to 100% when safety is not an issue; see Table 10–1) should be used throughout the course of therapy to ensure adequate concentrations reach the CNS. Duration of therapy for patients with infections of the CNS should be at least 10 to 14 days (Tunkel and Scheld, 1995). Four to 6 weeks of therapy is recommended in dogs (LaCouter and Child, 1995).

Adjuvant Therapy

Because of the harm associated with inflammation in a closed system, anti-inflammatories should be considered when treating CNS infections (e.g., meningitis). Corticosteroid therapy may be indicated during initial stages of treatment of meningitis to minimize the effects of inflammation and loss of capillary integrity (Tunkel and Scheld, 1995; LaCouter and Child, 1995). Experimentally, methylprednisolone decreases leukocyte accumulation, CSF outflow resistance, and brain water content in animals with bacterial meningitis (Tunkel and Scheld, 1995). Dexamethasone also reverses the development of brain edema and, compared with methylprednisolone, has the added advantage of decreasing CSF pressure and lactate. Note that these studies

Table 10–1. Doses of Antimicrobials Used to Treat Specific (Susceptible) Meningeal Infections in Human Patients Compared with Standard Dosing Regimens

	Dosing Regimen for CNS Infection		Standard Dosing Regimen	
Drug	***Dose[*]***	***Interval (Hours)***	***Dose***	***Interval (Hours)***
β-Lactams				
Penicillin G	24 million U/person	4	1–4 million U/person	4–6
	3 million U/kg	4	25,000–400,000 U/kg	4–6
Ampicillin	300 mg/kg[†]	6	0.25–0.5 g/person	4–6
Imipenem	2 g (28.5 mg/kg)	6	0.5–1 g/person	6
Aztreonam	6–8 g (86–105 mg/kg)	6–8	1–2 g/person	6
Third-generation cephalosporins[†]				
Cefotaxime	200 mg/kg	6–8	0.5–2 g/person	4–8
Ceftazidime	125–150 mg/kg	8		
Ceftriaxone	80–100 mg/kg	12–24	0.5–2 g/person	12–24
Aminoglycosides				
Amikacin	20–30 mg/kg	8[‡]	15 mg/kg	24
Gentamicin	3–5 mg/kg	8[‡]	3–5 mg/kg	24
Others				
Ciprofloxacin	800 mg (11.5 mg/kg)	12[§]	0.25–0.75 g/person	12
Trimethoprim/sulfamethoxazole	20 mg/kg[‖]	12	3–5 mg/kg[‖]	6–8
Doxycycline	200–400 g (30–60 mg/kg)	12	0.1 g/person	12
Chloramphenicol	4–6 g (57–86 mg/kg)	4–6	0.25–1 g/person	6
Rifampin	600 mg (8.5 mg/kg)[¶]	24	0.6 g/person	24

[*] Unless stated otherwise, dose is intended for IV administration. Dose on a g/person basis reflects total dose for a 70-kg person.

[†] For β-lactamase-negative organisms.

[‡] This interval was published in a 1995 textbook and likely does not reflect the currently recognized benefits to both safety and efficacy of once daily aminoglycoside dosing. Preferably, the total daily dose is given once daily. The safety of 90 mg/kg of amikacin has not been established for animals. Monitoring is recommended to guide therapy (at peak and one to two half-lives later).

[§] Efficacy of fluorinated quinolones is likely to be enhanced with once-daily dosing.

[‖] Based on trimethoprim component.

[¶] Oral dose.

did not include comparisons with antimicrobial therapy. Nonetheless, glucocorticoid therapy may be beneficial early during the course of therapy; indeed, treatment before antibacterial therapy may minimize the effects of mediators of inflammation released by dying bacteria (Tunkel and Scheld, 1995). Dexamethasone can be used (0.1 to 0.15 mg/kg every 6 hours up to 4 days), particularly in the presence of cerebral edema (Tunkel and Scheld, 1995). Treatment of cerebral edema should also include mannitol. For patients for whom monitoring is available, high-dose barbiturate therapy might be useful. Barbiturates decrease cerebral metabolic demands and cerebral blood flow and provide protection against oxygen radicals.

Adverse Reactions

Because of altered permeability of the blood-brain barrier, the infected CNS is more likely than the normal CNS to respond adversely to antimicrobials. Seizures are the most likely manifestation. Antibiotics most likely to cause seizures include selected β-lactams, most notably imipenem, metronidazole, and fluorinated quinolones, particularly in patients also receiving nonsteroidal anti-inflammatories. In general, seizures that develop as a result of drug therapy should be treated as with any acute seizural manifestation, with diazepam the preferred anticonvulsant of choice. Recommendations regarding dosing interval must be adhered to. β-Lactam antibiotics should be administered at both an increased dose and at frequent intervals and, ideally, via constant intravenous (IV) infusion.

Otitis Media

Otitis media associated with infection of the middle ear generally results from extension of otitis externa through a perforated eardrum (see later discussion of otitis externa) (Royschuk and Luttgen, 1995). A perforated eardrum may be hard to detect and must be distinguished from a "false" eardrum. Indications that infection of the external ear has extended into the middle ear include persistence of otitis externa, pain, swelling or narrowing of the ear canal, and evidence of neurologic involvement such as facial palsy (ptosis or paralysis of the lip or ear) or vestibular abnormalities. Less commonly, infection may follow extension from the pharynx via the eustachian tube or hematogenous spread. Radiographs and surgical exploration may be necessary for both diagnosis and treatment. Debris should be cytologically examined for evidence of predisposing conditions. Fungal infections (e.g., aspergillosis, infection caused by *Malassezia*), foreign bodies such as grass awns, neoplasia, inflammatory polyps, and tumors, including cholesteatoma, are among the more common causes of otitis externa. Calcification of auricular cartilage may also predispose the development of infection. Breeds apparently predisposed to otitis media include cocker spaniels and German shepherds.

Medical management of otitis media is often unsuccessful unless accompanied by surgical management, particularly if inflammation is severe and chronic or if the ear canal is stenotic. Surgical intervention may be the most cost-effective means of management and should provide the most accurate diagnosis. Treatment includes removal of debris and topical application of an antibiotic with or without a fungal preparation until the infection appears resolved. After debris is cleaned from the external canal, myringotomy (under general anesthesia) may be necessary to clean debris, collect a sample for culture and cytologic examination, and relieve pain associated with the infection. Systemic antibacterial therapy should begin in conjunction with topical therapy and continue for at least 4 to 6 weeks. For fungal infections (e.g., that caused by *Malassezia*), oral therapy with an imidazole antifungal (e.g., thiabendazole, ketoconazole, or itraconazole) should be implemented. For severe inflammation, glucocorticoids may be given topically or, if indicated, systemically for the first 1 to 3 weeks of treatment. Topical glucocorticoid therapy can be continued if inflammation persists after resolution of infection. Daily flushes of 5% acetic acid in water (1:1 to 1:3) may further control. Therapy must be continued until the tympanic membrane is repaired (generally 21 to 35 days). Control of the inflammatory process may be necessary before tympanic healing is complete. Should the tympanum not heal, debris may once again accumulate, and the ear must be flushed again. Surgical intervention may be necessary.

Otitis Interna

Otitis interna or labyrinthitis resulting from infection of the inner ear also occurs as a result of extension from otitis externa and media (see later discussion of otitis externa), movement of organisms through the eustachian tube, or hematogenous spread. Foreign bodies, tumors (including cholesteatoma), or other occlusive or inflammatory objects may predispose the development of infection (Braund, 1995). Clinical signs vary with the extent of vestibular dysfunction which in turn reflects the extent of infection and accompanying inflammation. Continuation of infection into the meninges is more likely in cats than in dogs.

Cultures that reflect infecting organisms might be obtained by sampling the middle ear; alternatively, myringotomy may be necessary. The most likely causative organisms include *Staphylococcus, Streptococcus, Proteus, Pseudomonas,* and *Enterococcus* species and *Escherichia coli.* Both topical and systemic antibiotic therapy should be implemented. Because yeast is often present, topical therapy should include antifungal drugs (e.g., nystatin). A number of antibiotics can be used for treatment of otitis interna. A lipid-soluble drug is preferred. Examples include the fluorinated quinolones and chloramphenicol. Many drugs are known to be ototoxic when applied directly to the middle or internal ear. Among them, the aminoglycosides in particular are recognized for potential ototoxicity. Other drugs or agents with known ototoxicity include fluorinated quinolones, erythromycin, polymyxin B, aspirin, and chlorhexidine (Pickrell et al., 1993). The lack of data regarding ototoxic potential should not be interpreted as potential safety. In general, direct application of any antibiotic to the external ear in the presence of a perforated eardrum should be avoided.

INFECTIONS OF THE MUSCULOSKELETAL SYSTEM

Osteomyelitis

Because bacterial myositis is rare unless it accompanies infection of the surrounding soft tissues, this discussion is limited to bacterial infections affecting the skeletal structures.

Pathophysiology

Similar to models described in humans (Mader and Calhoun, 1995), infections of the bone occur via a hematogenous route or secondary to a contiguous focus. Secondary osteomyelitis is further classified as that with or without vascular insufficiency. Both hematogenous and secondary osteomyelitis can also be classified as acute or chronic. Acute osteomyelitis is a suppurative infection accompanied by edema, vascular congestion, and small vessel thrombosis. Vascular supply to the site of infection becomes compromised as the infection extends into the soft tissue. Both medullary and periosteal blood supplies can become compromised, resulting in necrotic, ischemic, and, ultimately, dead bone, forming a sequestra. Bacteria located in this tissue become isolated, with acute osteomyelitis progressing to chronic osteomyelitis. Chronic osteomyelitis is characterized by a nidus of infected dead bone or scar tissue, an area of ischemic soft tissue, and a refractory clinical course. The risk of infection continues even in apparently cured osteomyelitis because of this nidus of infection. Indeed, the term *arrested* is often used in lieu of the term *cured* when referring to successful therapy in human patients.

In addition to the classes of osteomyelitis listed earlier, a more clinically relevant classification system has been developed in humans (Mader and Calhoun, 1995) which takes into account the status of the host, the anatomic considerations of the infection, treatment factors, and prognosis. Although the intent of this discussion is not to encourage a similar classification for animals, the characteristics of each stage serve as a means of delineating factors that complicate therapy in patients with osteomyelitis. Twelve distinct classes of osteomyelitis can be described by this classification scheme. Four stages are described based on anatomic considerations, with each stage characterized by additional complications.

Stage 1 (medullary) occurs early; the primary site of infection is endosteal or may include infected intramedullary pins. Therapy may simply include antibiotics but may also include surgical débridement or removal of the surgical foreign body. Stage 2 (superficial) osteomyelitis occurs as a result of extension of infection from soft tissue. As such, a secondary contiguous focus exists; this focus requires surgical débridement in conjunction with antibiotic therapy. Stage 3 (localized) osteomyelitis is characterized by full-thickness infection of the cortices with sequestration that requires surgical removal. Stage 4 (diffuse) osteomyelitis is diffuse and involves the full diameter of the infected bone and may cross a joint. Bone instability occurs as a result of either the infection or surgical treatment. Therapy includes débridement, management of dead space, and stabilization. Each of these four stages can be further categorized based on the status of the host: A (normal), B (local or systemic compromise), or C (treatment of the infection is more life threatening than the osteomyelitis). Local compromise includes chronic lymphedema, venous stasis, compromise of major vessels, arteritis, and extensive scarring fibrosis. Systemic compromise includes malnutrition, evidence of metabolic disease (e.g., renal or liver disease, diabetes mellitus), malignancy, age extremes, or immunosuppression. These stages are dynamic, being affected by therapy, progression of disease, and host status.

The metaphyses of long bones are the most common sites of hematogenous infection (Mader and Calhoun, 1995). Blood flow becomes slow and turbulent in this region, and capillaries lack phagocytic cells. Acute infection causes local cellulitis resulting in leukocyte accumulation, increased bone pressure, decreased pH, and reduced oxygen tension. Hematogenous osteomyelitis is usually caused by a single pathogenic organism, with *S. aureus* being a common pathogen. Vertebral osteomyelitis most commonly reflects a hematogenous source of infection, usually from an artery. Because each artery supplies two adjacent vertebrae, the infection usually involves two vertebrae. Again, *S. aureus* is a common infecting pathogen. Common sites of infection in humans that lead to vertebral osteomyelitis are the genitourinary tract, skin and soft tissue, respiratory tract, mouth, endocardium, and IV lines (Mader and Calhoun, 1995).

Contiguous infections generally result from direct inoculation of the bone due to trauma, extension from surrounding soft tissues, or contamination associated with surgery. Multiple pathogenic organisms are usually involved, and as in hematogenous infections, *S. aureus* is one of the most common organisms isolated. Gram-negative and anaerobic organisms are also commonly involved (Mader and Calhoun, 1995).

Chronic osteomyelitis is generally accompanied by local bone loss, persistent drainage, and sinus tracts. Surgical removal of the nidus of infection must accompany antibiotic therapy. Therapeutic success is less likely in the presence of necrotic surrounding soft tissue, bone instability, nonunion, or septic joints.

Therapy

Drug Movement Into Bone

Determining the extent of drug distribution to sites of infection in bone is not easy. Indeed, studies might require cannulation of nutrient artery and the ipsilateral femoral vein or, at the very least, detection of drug in bone. Recovery of drug from bones is, however, very difficult because tissue is lost during the extraction procedure, and not all drug is recovered. Likewise, clinical trials that document clinical efficacy are handicapped by variations in duration (acute versus chronic), the organisms studied, the model of osteomyelitis used, the mode of infection (in nonspontaneous models), the presence of foreign material, previous surgical procedures, and previous antibiotic therapy.

As with other sites of infection, drug penetration in osteomyelitis is determined by the molecular weight and the lipid solubility of the drug. Protein-bound drugs do not distribute to the site of infection. The mechanisms of capillary transport in osteomyelitic bone are similar to those in normal bone, although permeability ratios to the site of the drugs differ. A "blood-borne" barrier does not appear to exist. Volume of distribution studies have shown that generally concentrations of biologically active drug in the interstitial fluid space of normal cortical bone are equivalent to that in the serum. This implies that serum monitoring (and thus MICs) accurately depicts concentration at the primary site of drug-organism interaction (i.e., interstitial space) in the normal bone. This is also true for water-soluble drugs such as penicillins, cefamandole, and gentamicin. Doses of any antimicrobial may, however, need to be increased to overcome the response of the host to infection such as protein, tissue binding, and inactivation by host environment. Drug distribution into inflamed synovium occurs more rapidly and results in higher concentrations than in uninflamed joints. The characteristics of cefazolin result in its use for surgical prophylaxis in patients undergoing orthopedic surgical procedures (Cunha et al., 1984). Cefazolin readily traverses capillaries of both normal and osteomyelitic bone, and the pathophysiology of osteomyelitis enhances penetration. Although the volume of spaces (plasma and interstitial) increases in osteomyelitis by 330% and 941%, respectively, the distribution of cefazolin increases proportionately. Cefazolin concentrations in bone parallel those in plasma. Cefazolin is not as highly protein bound in dogs as in humans (35% vs. 80%), which should result in higher concentrations of pharmacologically active drug in the bone tissues of dogs.

In an attempt to increase drug concentrations at the site of osteomyelitis, methods by which drugs can be directly deposited have been devised. Gentamicin-impregnated acrylic bone cement or acrylic beads have proved effective both experimentally and in spontaneous osteomyelitis. Other advances included antibiotic-impregnated plaster of Paris and hydroxyapatite. The clinical efficacy of these methods of drug delivery have not, however, been well documented in veterinary medicine. The importance of surgical débridement, dead space management, and, when indicated, stabilization to treatment of osteomyelitis cannot be overemphasized. Culture and susceptibility testing provides the best basis for antimicrobial selection; inappropriate antibiotic therapy may result in the extension of disease, necrosis, and sequestrum formation.

Antimicrobial Selection

Although drug distribution to healthy bone is adequate, the detrimental effects of osteomyelitis minimize drug distribution to the site of infection. In experimental rabbit models of osteomyelitis caused by *S. aureus,* drugs characterized by the best bone to serum ratio were, in order, clindamycin, vancomycin, molaxatam (a β-lactam antibiotic), tobramycin, cefazolin, and cephalothin (Mader and Calhoun, 1995; Table 10–2). Fluorinated quinolones were not studied. Parenteral antibiotic therapy should begin with drugs targeting the most likely organisms; drug therapy can be changed if indicated based on susceptibility data. Because bone revascularization takes 4 to 6 weeks, antibiotic therapy should occur for a similar time to protect the bone as it revascularizes. The first 2 weeks of therapy should be via parenteral administration (data from the start of therapy or after surgical débridement). For acute hematogenous osteomyelitis, the causative agent must be properly identified. Mismanagement with inappropriate antibiotics can lead to extension of the infection, necrosis, and the formation of sequestra. If the patient has not responded to specific antimicrobial therapy (i.e., based on culture) within 48 hours, surgical intervention is indicated for human patients. Bone biopsy specimens are necessary for culture for human patients (Mader and Calhoun, 1995) unless the patient also has positive blood cultures. For chronic osteomyelitis, parenteral administration should occur for the duration of therapy. Because of its excellent distribution characteristics, oral quinolone therapy may be an acceptable alternative for gram-negative and *Staphylococcus* infections. Note, however, that the activity of the fluorinated quinolones against anaerobes and other gram-positive organisms (e.g., *Streptococcus,* some *Corynebacterium*) is less predictable. In addition, although bone concentrations of difloxacin are high (see package insert), concentrations do not decline over time, suggesting that the drug is bound and thus inactive. Studies are needed to document the efficacy of this drug for treatment of osteomyelitis. Clindamycin or amoxicillin-clavulanic acid can be used in combination with the quinolones to provide gram-positive and anaerobic coverage.

Chronic contiguous osteomyelitis may be particularly difficult to resolve. Assessment of vascular integrity by cutaneous oxygen tension can be useful for determining the extent of damaged tissue to be removed (Mader and Calhoun, 1995). Hyperbaric oxygen therapy may facilitate healing in tissues characterized by low oxygen tension. Dead space can be managed short term with antibiotic-impregnated acrylic beads; the beads are generally replaced with a cancellous bone graft after 2 to 4 weeks. Hyperbaric oxygen is an important adjunct therapy for human patients with osteomyelitis. It serves to restore intramedullary oxygen tension and thus facilitates phagocytic killing. Furthermore, it supports collagen production, angiogenesis, and wound healing (Mader and Calhoun, 1995).

Infections associated with prosthetic devices involving cement are particularly problematic to resolve. Infections generally occur at the bone-cement interface. Infectious pathogens are numerous and, in humans, often include microorganisms considered to be contaminants of cultures (e.g., corynebacteria, propionibacteria, and *Bacillus*). Polymethylmethacrylate cement may predispose the site to infection because it can inhibit phagocytic function. Heat induced by the polymerization reaction can damage tissues, although this might be minimized by flushing the area with sterile normal saline. Host response to the cement may also facilitate infection by *S. aureus,* and microorganisms can secrete materials that protect against host defense mechanisms. Infection can be treated with removal of the prosthetic device and 6 weeks of antimicrobial therapy followed by reimplantation or surgical removal and débridement with immediate reimplantation accompanied by methylmethacrylate cement inpregnated with an antibiotic (an aminoglycoside). When the prosthesis cannot be removed, life-long antibiotic therapy has been implemented for human patients, assuming that the microorganism is suffi-

Table 10–2. Concentrations of Selected Antibiotics in Bone Experimentally Infected with *Staphylococcus aureus*

Drug	Dose	Concentrations (μg/mL)		Bone to Serum Ratio	Breakpoint MIC
		Serum	*Bone*		
β-Lactams					
Nafcillin	40 mg/kg	21.9	2.1	0.095	≤2 to ≥4
Moxalactam	40 mg/kg	65.2	6.2	0.095	≤8 to ≥64
Cefazolin	5 mg/kg	45.6	3.2	0.07	≤8 to ≥32
	15 mg/kg	67.2	2.6	0.04	≤8 to ≥32
Cephalothin	40 mg/kg	34.8	1.3	0.04	≤8 to ≥32
Aminoglycosides					
Tobramycin	5 mg/kg	14.3	1.3	0.09	≤4 to ≥16
Others					
Clindamycin	70 mg/kg	12.1	11.9	0.98	≤0.5 to ≥4
Vancomycin	2–3 g (28.5–43 mg/kg)	35	5.3*	0.15	≥14

*Monitoring recommended.

Adapted from Mader JT, Calhoun J: Osteomyelitis. In Mandell G, Bennett JE, Dolin R (eds): Principles and Practice of Infectious Diseases, 4th ed, pp 1039–1050. New York, Churchill Livingstone, 1995.

ciently susceptible to oral antibiotic therapy and the patient can tolerate the therapy.

Septic Arthritis

Pathophysiology

Septic arthritis most commonly reflects hematogenous inoculation. Patients with osteoarthritis or immune-mediated arthritis, trauma, or intra-articular injection are predisposed to infections in the inflamed joint. Trauma may predispose to infection because of a loss of vascular integrity. Synovial tissue is very vascular, and the lack of a basement membrane facilitates bacterial penetration. Bacteria can contribute to the process of inflammation through production of tissue-damaging mediators such as proteases. *S. aureus* is among the organisms most commonly causing infection in humans, in part because of its ability to bind to bone sialoprotein, a glycoprotein of joints (Smith and Piercy, 1995). It is able to contribute to destruction of cartilage because of the production of chondrocyte proteases. Infection often affects a single joint and usually is limited to the joint. Exceptions are made in the presence of predisposing factors that affect multiple joints (e.g., immune-mediated arthritis).

Clinical signs associated with septic arthritis include fever, limited joint motion, and swelling of peripheral joints associated with joint tenderness. Synovial fluid analysis discriminates between septic and nonseptic causes of arthritis. In general, septic arthritis more commonly is associated with increased polymorphonuclear leukocytes. The presence of immunomodulating drugs (e.g., glucocorticoids) may blunt leukocyte infiltration. In human patients, the presence of bacteria can be detected in approximately 33% of cases by cytologic examination of a smear of synovial fluid. Cytologic examination should include Gram stains. Synovial fluid should be cultured; for human patients, blood culturing also is recommended (Smith and Piercy, 1995). False-negative cultures may not, however, rule out bacterial arthritis; in human patients with documented infection, synovial fluid cultures were negative 10% of the time. Radiographic examination may help rule in arthritis.

The most common causes of septic arthritis reported in animals are bacterial in origin. The potential for viral causes should not be ignored. In human patients, two syndromes of arthritis are described: acute and chronic, monarticular. The syndromes are caused by different types of organisms, with mycobacterial or fungal infections of the joint largely responsible for the chronic form.

Therapy

Antimicrobial Selection and Treatment

In human patients, septic arthritis is aggressively treated. Empirical therapy is begun after culture collection using an intravenously administered drug effective against *S. aureus*. Examples include cefuroxime, cefotaxime, and ceftriaxone. The use of fluorinated quinolone is questionable in the presence of joint damage; the impact on healing cartilage may be similar to that of cartilage in growing animals. Response to antimicrobial therapy is based, in humans, on repetitive analysis of synovial fluid collected by joint aspiration. Persistence of infusion beyond 7 days is interpreted as the need for surgical drainage.

Use of appropriate antimicrobials early in the course of arthritis will minimize damage to the joint. Weight bearing on the infected joint should be minimized, although immobilization is not necessary. Passive motion should be instituted once pain has subsided. Weight bearing can begin when inflammation has resolved. Residual damage may occur in up to 30% of human patients (Smith and Piercy, 1995).

Adjuvant Therapy

Because septic arthritis can be accompanied by the loss of collagen and erosion of articular surfaces, therapy with disease-modifying agents should strongly be considered. Injectable products such as polysulfated glycosaminoglycans (ADEQUAN), pentosan polysulfate, and hyaluronic acid (the latter perhaps in combination with either of the former) are more apt to act more rapidly. Oral disease-modifying agents such as chondroitin sulfates, keratan sulfates, and glucosamines (e.g., Cosequin) also should be strongly considered until such time as the joint is healed.

RESPIRATORY TRACT INFECTIONS

Pathophysiology

A major barrier to passive drug movement from the blood to the site of infection in the respiratory tract is the bronchial-alveolar-blood barrier (Bergogne-Bérézin, 1988; Braga, 1989). Whereas drugs of a molecular weight up to 1000 can move easily through the open junctions of the capillaries, drugs must passively diffuse through the tight junctions of the alveolar epithelial cells (Bergogne-Bérézin, 1988). Movement of drugs into bronchial secretions occurs primarily by passive diffusion and is more likely to occur for drugs with favorable physiochemical characteristics such as high lipophilicity and low molecular weight (<450). Few drugs achieve concentrations in respiratory tissues equal to concentrations in the plasma. Thus, achieving simply the MIC in the plasma against an organism infecting the respiratory tract is likely to result in therapeutic failure (Levin and Karakusis, 1984; Bergan, 1981). Rather, the targeted plasma drug concentration must be great enough to ensure that the MIC will be reached at the site of infection. The relationship between plasma and bronchial drug concentrations can be described by the partition ratio (Bergogne-Bérézin, 1988; Braga, 1989), which is the area under the time plasma drug concentration versus time curve in plasma divided by the same in bronchial secretions. Such a relationship would compare not only peak concentrations but also the time that drug stays in tissues, which generally is longer than in plasma. Collection of sequential bronchial secretion samples necessary for kinetic analysis is, however, difficult, and such information currently is not available for many drugs. A more practical relationship is the ratio of bronchial drug concentrations to plasma drug concentrations. This ratio has been established for a number of antimicrobial drugs and is often available in package inserts or textbooks. The ratio can serve as a basis for antimicrobial selection and dose manipulation (Bergogne-Bérézin, 1988; Braga, 1989).

Among the antimicrobial classes, the penicillin antibiotics are characterized by one of the poorest plasma to bronchial tissue drug concentrations (mean of 9%), although variation exists among the individual drugs (Table 10–3). For example, amoxicillin reaches four to five times higher concentrations in bronchial secretions than ampicillin when given at the same dose, although this is probably due to higher plasma concentrations (Bergogne-Bérézin, 1988; Braga, 1989). Only about 30% of either drug in plasma, however, reaches bronchial secretions. The cephalosporins are distributed slightly better than the penicillins (mean of 15%), again with variation among the individual members. For example, cephalexin achieves only 15% of plasma concentrations, whereas cefoxitin and cefotaxime reach 25% of plasma concentrations. Selected third-generation cephalosporins may reach even higher concentrations. Imipenem also has one of the better distribution patterns of the β-lactam antibiotics, reaching 20% of plasma concentrations in bronchial secretions (Bergogne-Bérézin, 1988; Braga, 1989).

Table 10–3. Ratio of Serum to Bronchial Concentrations of Antibiotics 2 to 3 Hours After Administration in Humans

Antibiotics	Bronchial to Serum Ratio (%)
Amikacin	24.5
Ampicillin	3
Amoxicillin	3.5
Clavulanate	16.9
Cefoxitin	24
Cefotaxime	25
Ciprofloxacin	48
Clindamycin	61
Doxycycline	38
Erythromycin	41–43
Gentamicin	27
Imipenem	20
Sulfamethoxazole	18
Trimethoprim	100

The aminoglycosides distribute into bronchial secretions somewhat better than the β-lactams, generally reaching about 30% of plasma concentrations. Clindamycin achieves 61% of plasma concentrations. Tetracyclines, and particularly doxycycline (38%) and minocycline, can reach 30% to 60% of plasma concentrations after a single dose. Macrolides such as erythromycin generally distribute well into bronchial secretions (41% to 43%), although newer drugs such as azithromycin (which can accumulate up to 200-fold in pulmonary tissues) distribute much better than erthromycin (Bergogne-Bérézin, 1988; Braga, 1989). The fluorinated quinolones reach 70% or more of plasma concentrations; they also accumulate over 50- to 100-fold in alveolar macrophages. The potentiated sulfonamides have variable distribution. Whereas trimethoprim reaches 100% of serum concentrations in bronchial fluid, the sulfonamide component may achieve much lower concentrations. For example, sulfamethoxazole achieves only 18% of serum concentrations. Metronidazole, useful for anaerobic infections, achieves 100% of plasma concentrations in respiratory secretions (Bergogne-Bérézin, 1988; Braga, 1989). For drugs with a long elimination half-life (e.g., doxycycline), the ratios of bronchial concentrations to plasma concentrations may increase with repetitive dosing as drugs accumulate (Bergogne-Bérézin, 1988; Braga, 1989).

Inflammation generally increases concentrations of selected antibacterials (e.g., β-lactams and aminoglycosides) in bronchial secretions due to local vasodilation and vascular permeability. Excessive inflammation can, however, preclude antibiotic distribution (Fig. 10–1) (Bergogne-Bérézin, 1988; Braga, 1989). Mucus produced in response to a bacterial infection in the respiratory tract can also interfere with antimicrobial therapy (Bergogne-Bérézin, 1988; Braga, 1989). Aminoglycoside efficacy may be decreased by chelation with magnesium and calcium in the mucus. Antibiotics may bind to glycoproteins, and mucus may present a barrier to passive diffusion. In addition, some antibiotics may alter function of the mucociliary apparatus, either by increasing mucous viscosity or decreasing ciliary activity (e.g., tetracyclines). Because of these negative effects, drugs that decrease mucous viscosity (e.g., expectorants or bromhexine, a drug available outside of the United States) or are mucolytic (e.g., acetylcysteine) may facilitate antibiotic therapy (Bergogne-Bérézin, 1988; Braga, 1989). *N*-acetylcysteine may be given by any route and reach effective concentrations in the lung. In addition to its muco-

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Figure 10–1. The accumulation of inflammatory debris in the peribronchiolar region *(A)* or in the alveolus *(B)* is likely to impair drug distribution to the site of infection and may hinder the activity of the drug that is able to penetrate the debris. (Photograph courtesy of Bayer Animal Health.)

lytic effects, the drug imparts some anti-inflammatory effects (oxygen radical scavenging) and appears to help bacterial penetration of the mucopolysaccharide capsule of gram-negative bacteria. Human patients are dosed with 250 to 500 mg orally a day (the drug is available in granular form in Europe, but the solution can also be administered orally). We have used from 125 mg total dose to up to the dose used to treat acetaminophen toxicosis (144 mg/kg IV followed with 70 mg/kg every 8 to 12 hours) in severe cases.

Bacterial Tracheobronchitis

Bordetella bronchiseptica is the primary bacterial pathogen associated with infectious tracheobronchitis in dogs. This contagious disease, characterized by paroxysms of coughing, generally is mild and self-limiting but can become serious, particularly if multiple bacteria become involved. The respiratory tract has a very functional mucosal defense mechanism that generally is able to clear most organisms within 3 days of infection. *Bordetella* will, however, persist for up to 14 weeks after infection (Thayer, 1984; Hawkins, 1995). Active attachment to cilia and ciliostasis induced by *Bordetella* appear to be important reasons for bacterial persistence. Whereas the disease generally is self-limiting to 7 to 10 days' duration, systemic signs indicative of pneumonia indicate the need for antibiotic therapy.

Therapy should be based on culture and susceptibility data because organisms other than *Bordetella* frequently complicate infection. Antimicrobial therapy should, however, include a drug with known efficacy against *B. bronchiseptica* (see later discussion). It is likely that *Mycoplasma* species also play a role in infectious tracheobronchitis in dogs, and drug selection should include this organism. Because of the location of the organism and the difficulty of drug penetration into bronchial secretions, aerosolization of selected antimicrobials (aminoglycosides, polymyxin B) should be considered as an adjunct to systemic antibiotic therapy. Systemic therapy should include a drug that penetrates bronchial secretions well. Drugs with known in vitro efficacy against both *B. bronchiseptica* and *Mycoplasma* include the fluorinated quinolones, doxycycline or minocycline, chloramphenicol, and the macrolides. Among these, only the fluorinated quinolones typically are associated with bactericidal concentrations. Accumulation of the macrolides in lung tissue may, however, result in bactericidal concentrations of these otherwise bacteriostatic drugs. Vaccination should be used to immunize dogs against the primary pathogens of infectious tracheobronchitis.

Bacterial Pneumonia

Bacterial pneumonia is much more common in dogs than in cats. Although *B. bronchiseptica* and *Streptococcus zooepidemicus* are among the bacterial organisms commonly associated with pneumonia, many other organisms can cause infection, including *E. coli, Pasteurella, Klebsiella, Staphylococcus,* and *Pseudomonas* (Hawkins, 1995). The potential for *Mycoplasma* species and anaerobic organisms (particularly in the presence of abscessation) as a cause of infection should not be ignored. Generally, the respiratory tract is sterile below the larynx. Cytology and culture collected by tracheal wash, bronchoscopy, bronchial lavage, or lung aspiration should serve as the basis for treatment. Cultures of the pharyngeal area should not be the basis of antimicrobial selection for infections of the respiratory tract. Susceptibility data should be compared to select the most appropriate antimicrobial. The more severe the infection, the more important lipid solubility becomes to drug selection. Doses should be sufficiently high to establish bactericidal concentrations of drug at the site of infection. Among the antimicrobials, fluorinated quinolones such as enrofloxacin should be considered because of their spectrum and lipid solubility. In addition, accumulation by alveolar macrophages might enhance drug distribution at the site of inflammation (Hawkins et al., 1998). Accumulation has been documented for both enrofloxacin and marbofloxacin. Combination therapy should be considered to not only broaden the spectrum of antimicrobials but also to enhance efficacy. Aerosolization should be considered in addition to (never in lieu of) systemic antimicrobial therapy, particularly in severe cases. Aerosolization may be particularly important for infections associated with *B. bronchiseptica.*

Mobilization of respiratory secretions may be important to resolution of infection. In addition to physical techniques such as coupage, mucolytic and mucokinetic agents should be administered. Bronchodilators may also facilitate movement of respiratory secretions as well as facilitate airway movement. Their use is controversial, with some authors suggesting that their anti-inflammatory effects may be detrimental. Control of inflammation without the use of more direct immunosuppressants (such as glucocorticoids), however, may not be serious enough to outweigh the potential benefits of airway relaxation. Theophylline can cause ventilation perfusion mismatching, and oxygen therapy should be available to patients when this drug is administered in moderate to severe cases. Alternatively, β_2-selective bronchodilators such as terbutaline should be considered. The author has used a combination of theophylline and terbutaline in severe cases of bronchopneumonia associated with hypoplastic trachea in a pediatric patient. Mucomyst *N*-acetylcysteine (200 to 500 mg orally or IV twice daily) should be considered for adjuvant therapy in infections associated with marked inflammatory debris. Drug penetration through mucoid debris present at the site of infection as a result of the microbe will be decreased, facilitating antimicrobial penetration. Penetration of the lipopolysaccharide membrane of gram-negative organisms will likewise be enhanced. Treatment should continue until resolution of radiographic signs indicative of pneumonia, which may require up to 6 weeks.

Pyothorax

Pyothorax, otherwise known as *empyema,* refers to the accumulation of white blood cells in the pleural space (Bauer and Woodfield, 1995). Organisms reach the pleural space either by direct introduction (most commonly via a foreign body) or by hematogenous or lymphatic spread. The physiologic forces that keep the pleural space essentially free of fluid are overcome by inflammation, resulting in an increase in regional blood flow, capillary hypertension, increased capillary permeability, and increased oncotic draw (by inflammatory proteins) of fluid into the pleural space. Lymphatic drainage becomes progressively more important as oncotic draw into capillaries is lost, but accumulation of inflammatory debris and fibrosis ultimately preclude lymphatic drainage of the pleural space. Gram stain of fluids collected via thoracentesis can be a most rapid method of diagnosing the bacterial cause of infection. The incidence of anaerobic organisms as either sole agents (particularly in cats) or in combination with other bacteria is high. Thus, samples submitted for culture should include both aerobic and appropriately collected anaerobic specimens. The presence of a foul smell (reflecting the production of organic matter by-products) is supportive of infection by anaerobic organisms. In order of frequency, causative species in the cat include *Bacteroides* (15%), *Actinomyces* (including *Nocardia*), *Peptostreptococcus, Pasteurella, Fusobacterium,* and *Mycoplasma.* Causative organisms in the dog include *Fusobacterium, Actinomyces* (including *Nocardia*), *Corynebacterium, Streptococcus, Bacteroides, Pasteurella, E. coli, Klebsiella,* and *Peptostreptococcus* (Bauer and Woodfield, 1995). Fungal organisms also should be considered as a cause of pyothorax.

Removal of inflammatory debris is a critical component of effective antimicrobial therapy for the patient with pyothorax. Drainage by thoracentesis alone is not likely to be effective; indeed, up to 80% mortality can be expected with this approach. Progression to a chronic stage can be expected in many patients in whom drainage has been inadequate, increasing both mortality and cost compared with the patient with adequate drainage. Thus, therapy should include chest tube drainage (preferably by continuous water seal suction at 20 cm). Bilateral chest tube placement may be necessary in some patients. Adequate hydration minimizes the risk of hypotension or apnea induced by continuous suction. Effective removal of debris not only will remove mediators associated with morbidity but also will facilitate antimicrobial distribution. Response to antimicrobial therapy should be based on repeated cytology and Gram stains. Clinical signs and cytologic findings should improve once chest tube drainage is in place. Bacteria generally are nondetectable 2 to 3 days after therapy is begun; however, serial cultures should be used to confirm the absence of growth. Antimicrobial selection should be based on culture and susceptibility data. Unfortunately, growth often does not occur despite cytologic evidence of bacteria. An anaerobic environment should be assumed even if aerobes are cultured because many of these organisms are able to survive and grow in an anaerobic environment.

Antimicrobials that are not effective in an anaerobic environment (e.g., aminoglycosides) should not be used as sole agents in the treatment of pyothorax. A penicillin should be included in the initial therapy because the spectrum includes anaerobic organisms and synergistic interactions that occur with a number of antimicrobials. An aminopenicillin (ampicillin, amoxicillin) is preferred to penicillin in order to extend the spectrum to include more gram-negative organisms. In severe cases, an extended β-lactam (e.g., imipenem) should be considered. Because many of the organisms (including anaerobes) associated with pyothorax produce β-lactamases, protected drugs or drugs inherently resistant to β-lactamases should be selected. The use of cephalosporins for the treatment of pyothorax probably should be avoided because their efficacy against anaerobes is less than that of penicillins. The aminoglycosides (particularly amikacin) are among the drugs to which *Nocardia* and *Actinomyces* are very susceptible and should be considered in combination with a β-lactam.

For initial therapy, particularly in serious cases, the author prefers a combination of parenteral (IV) amoxicillin/ampicillin or ideally imipenem if its cost is not prohibitive, particularly in serious cases, and amikacin. Ampicillin should be given at a high dose at least every 6 hours and preferably every 4 hours. Amikacin should be given once daily. Therapy should be continued for 7 to 10 days. At that time, assuming improvement is evident, oral therapy can be implemented. The author prefers high doses of amoxicillin/clavulanic acid (every 8 hours) and a sulfadiazine/trimethoprim combination (30 to 45 mg/kg twice daily) based on both drugs. Synergistic actions against *Nocardia* have been documented (in vitro) with a number of antimicrobial combinations, including amikacin and sulfadiazine/trimethoprim (Eliopoulos and Moellering, 1996).

Other drugs that have shown efficacy against *Nocardia* or *Actinomyces* and are characterized by adequate distribution to the pleural space include clindamycin, minocycline, and doxycycline (Eliopoulos and Moellering, 1996). Precaution is advised, however, when using these bacteriostatic drugs in combination with a bactericidal drug.

URINARY TRACT INFECTIONS

Pathophysiology

Bacteriuria simply refers to the presence of bacteria in the urine. Significant bacteriuria has been defined as bacteria present in the urine in numbers exceeding the amount caused by contamination from the urethra ($\geq 10^5$ bacteria or colony forming units/mL). Therapy is indicated for infections associated with bacteria that exceed this amount. Infections of the urinary tract (UTI) include but are not limited to pyelonephritis, uretitis, cystitis, urethritis, and prostatitis. Infection occasionally is restricted to urine (bacteriuria) (Lulich and Osborne, 1995). Because infection in any region of the urinary tract can be accompanied by or result in infection throughout the tract, however, terminology inclusive of all sites often is preferred to terms limited to a single site of infection (e.g., upper or lower urinary tract infection).

The clinical signs of UTI are variable with the site of infection. As with other body systems, the inflammatory response largely is responsible for the clinical signs of UTI. Bacteriuria can be asymptomatic, detected on urinalysis but causing no clinical signs. Bacteriuria also might be asymptomatic (Sobel and Kaye, 1995). Acute cystitis can cause dysuria but rarely causes signs of systemic inflammation. Acute pyelonephritis, however, is often associated with signs of systemic inflammation, including fever. As in any body system, evidence of inflammation is not necessarily evidence of infection and the need for antimicrobial therapy. Likewise, absence of inflammation does not rule out bacterial infection. The incidence of UTI in dogs is higher (estimated at 14%) than that in cats (1% to 3%) (Lulich and Osborne, 1995). Identification of the site of UTI may be difficult, as might be discrimination of the infection as primary or secondary.

Generally, the urinary tract is sterile above the urethra. Infection of the urinary tract begins with bacterial adherence to uroepithelial cells of the urinary mucosal surface. Adherence is a specific two-phase process involving bacterial surface structures, referred to as *adhesins*, and complementary receptors of the epithelial cells (Sobel and Kaye, 1995). Bacterial adhesins are generally located in the bacterial fimbriae, although they occasionally are expressed in the absence of fimbriae. Species differences exist among the types of receptors in the host epithelial cells. The predominant receptor type in humans is glycolipid in nature, and its presence varies with blood cell types, implying individual variation in susceptibility to bacterial adherence in several body systems. *Escherichia coli* contains adhesins that bind to the glycolipid receptors. Mannose-containing receptors also have been documented in humans; both *E. coli* and non–*E. coli* are characterized by mannose-specific adhesins. These adhesins are present on most Enterobacteriaceae. On entry into the lower urinary tract, mannose adhesins appear to be important for colonization of the bladder or lower structures. In contrast, mannose-resistant fimbriae and other adhesins appear to be critical for colonization of the renal structures. *Escherichia coli* from canine UTI appear to adhere primarily through mannose-sensitive adhesins. Binding between receptor and adhesin results in changes in the receptor-bearing cell. Toxins such as endotoxin may act in conjunction with adherence to induce inflammation. Treatment with mannose or similar molecules may block the receptors, thus reducing adherence (Senior, 1985). The severity of a UTI may be correlated with the adherence to uroepithelial cells. Organisms causing acute pyelonephritis in human patients are characterized by higher adherence compared with organisms causing asymptomatic bacteria. These *E. coli* produce a number of virulent factors, including hemolysin and aerobactin, and are able to resist the antibacterial effects of serum (Senior et al., 1992).

Several antimicrobials interfere with bacterial expression of fimbrial adhesins and thus may prevent bacterial attachment and colonization. Examples include penicillin, ampicillin, amoxicillin, and streptomycin. Single daily administration of antibiotics at reduced (one half to as little as one eighth) also may be able to prevent UTIs because of interference with fimbrial expression or formation (Senior, 1985).

A number of other microbial factors increase the risk of UTI (Lulich and Osborne, 1995). These include but are not limited to other microbial antigens, production of toxins such as hemolysin or urease, and the mucoid polysaccharide capsules (e.g., *Pseudomonas*). Indeed, bacterial infection is rarely the initial cause of disease of the lower urinary tract in cats, but development of infection is a common sequela (Lees, 1996a). The role of viruses in feline lower urinary tract disease has been reviewed (Kruger et al., 1996). Viruses that have been isolated in the urinary tract of cats with spontaneous disease include feline calicivirus, bovine herpesvirus 4, and feline syncytia-forming virus (Kruger and Osborne, 1993). Other potential uropathogens include mycoplasmas and ureaplasmas (Kruger and Osborne, 1993; Senior and Brown, 1996). Causes of recurrence or reinfection of the lower urinary tract are discussed below.

A number of host factors prevent or limit bacterial infection in the bladder (Sobel and Kaye, 1995). Whereas asymptomatic bacteriuria will often resolve or become self-limiting if left untreated, bacterial pyelonephritis is likely to progress (Lulich and Osborne, 1995; Senior et al., 1992). The normal flora of the vulva and prepuce may be an important host defense mechanism against infecting microorganisms of the urinary tract. Normal flora may prevent colonization by pathogenic organisms or disrupt metabolism of pathogens. Secretory antibodies may coat infecting organisms, preventing adherence, and reduced antibody production may promote infection. The mucus may have other antibacterial effects. In the bladder, mucosal secretion of surface mucopolysaccharides is important to host defense by preventing attachment of bacteria. Destruction of this layer facilitates infection. Treatment with sulfonated glycosaminoglycans intraluminally may coat the uroepithelium and thus provide a barrier to bacterial adherence.

Administration of carbenoxolone (a licorice derivative) stimulates secretion of mucosal polysaccharide and, in rabbits and humans, increases the clearance of *E. coli* infection. In the bladder, the composition of urine can affect bacterial growth. Concentration (unless extreme) of urine is not likely to affect bacteria (bacteria are generally hypertonic compared with their environment), but high concentrations of urea or other compounds or low pH may impair bacterial growth. The addition of prostatic fluid inhibits bacterial growth. Exceptions include selected *Staphylococcus* and *Proteus* species, which are relatively resistant to the antibacterial effects of urea (Sobel and Kaye, 1995). Tamm-Horsfall protein secreted by the cells of the ascending loop of Henle binds to *E. coli* via mannose-containing side chains and, as such, probably acts as a urinary bacterial defense mechanism. Other factors that help prevent or reduce bacterial infection include frequent urination, a small residual urine volume in the bladder, and rapid urination.

Recurrences reflect either relapses or reinfections (Sobel and Kaye, 1995). Possible sources of UTI include ascension from the urethra and hematogenous and lymphatic factors. Ascending infection is by far the most common route of infection, although the kidney is predisposed to develop infection associated with blood-borne organisms. In humans, the origin of bacteria infecting the urinary tract is generally fecal, with the frequency of infection by a particular strain depending on the virulence of the organism. Pathogens generally travel along the urethra to the bladder. Anatomic deformity and turbulent urine flow may facilitate antegrade movement of organisms toward the bladder. Catheterization is a common cause of ascension of bacteria from the urethra to the bladder. In human patients, one catheterization results in infection in 1% of patients; and infection develops in most if not all patients within 3 to 4 days of placement of an indwelling, open drainage catheter system (Sobel and Kaye, 1995). Female patients are more predisposed to ascending infection due to the shorter length of the tract and increased risk of contamination. Once in the bladder, infection can continue to ascend up the ureter to the kidney, particularly if vesiculoureteral reflux is present.

In an experimental model of UTI in cats, catheterization increased the risk of persistent UTI in cats with cystitis despite the use of a closed system of urine drainage (Barsanti, 1998). Other factors may contribute to recurrence or reinfection. Use of glucocorticoids and urinary tract catheterization were two therapeutic factors that contributed to an increased risk of UTI in an experimental model of male feline cystitis (Barsanti, 1998). A study of infection in cats after perineal urethrostomy found that while the surgical procedure does not predispose the cat to recurrent bacterial urinary tract infection, surgical alteration of the urethral surface coupled with underlying uropathy may increase the risk and thus prevalence of ascending infection (Griffin and Gregory, 1992). Catheters should be used only in cats for which obstruction is likely if catheterization is not performed (Lees, 1996b). Urinary calculi may contribute to feline lower UTIs. One study reports growth of bacteria in urine or calculi of 41% of cats with urinary calculi (Ling et al., 1990). *Staphylococcus* was responsible for most (45%) of these infections. Pyometra may serve as a source of reinfecting organisms (Wadas et al., 1996) as might tumors (e.g., transmissible venereal tumors) (Batamuz and Kristensen, 1996).

Therapy

Sequelae of Drug Therapy

The goal of drug therapy is to eliminate bacteriuria. However, four sequelae of therapy may occur (Sobel and Kaye, 1995; Lulich and Osborne, 1995). *Cure* can be defined as negative urine cultures during and after (usually 1 to 2 weeks) antimicrobial therapy. Quantitative bacterial counts should decrease within 48 hours after initiation of an appropriate antimicrobial. Cure does not rule out the possibility of reinfection. Urinary tract infections may reflect first time or recurrent infections. *Chronic UTI* is often used to refer to persistence of infection. The terms recurrence, persistence, and relapse seem to be used interchangeably when referring to UTIs. *Persistence*, or recurrence, can refer to presence of significant or low numbers of bacteria after 48 hours of therapy. If the numbers are significant, then antimicrobial resistance or insufficient drug concentrations (e.g., improper dose, poor oral absorption, poor renal elimination) should be suspected. If numbers are very low, a continuous source of bacteria in the urinary tract (e.g., urinary calculi, prostate, kidney) or contamination from the lower urinary tract should be suspected (Sobel and Kaye, 1995). In such cases, cultures can identify persistent organisms after therapy has been discontinued. An appropriate approach would be classification of recurrent or persistent infections into three sources.

Relapse occurs when the same organism causes infection within 1 to 2 weeks after therapy has been discontinued. Relapse generally occurs within 1 to 2 weeks of cessation of therapy and may reflect either a very deep-seated infection or an abnormality of the urinary tract (e.g., structural, renal, or prostatic infection). The presence of a different organism is considered *reinfection*, that is, a new infection. A new infection also can occur by the same organism located outside of the urinary tract. Generally, reinfection occurs more than 1 to 2 weeks after cessation of therapy. *Superinfection* may also occur and reflects infection with an additional organism during the course of antimicrobial treatment (Lulich and Osborne, 1995). Evidence of persistent, relapsing, or superinfections should lead to more aggressive therapy and to the use of bactericidal rather than static drugs. Among the common causes of complications associated with UTI, antimicrobial resistance, unidentified underlying disease, and inappropriate dosing regimen should be considered.

Antimicrobial therapy should be used only when reasonable evidence of infection exists. Bacterial UTI occurs much less frequently in cats than in dogs, and clinical signs indicative of cystitis should not be interpreted as a need for antimicrobial therapy. Selection of the proper drug is complicated by host factors, severity of infection, cost and convenience considerations, and the plethora of antimicrobial drugs available from which to select.

Identification of the Target

In human patients, diagnosis of UTI in asymptomatic patients is based on at least two clean-catch midstream urine collections. The same organism should be present in significant (see earlier) amounts in both cultures. A single culture is sufficient in the presence of symptoms. Urinary cultures should be the basis of antimicrobial selection in complicated infections (e.g., reinfection or relapse; history of antimicrobial use within the past 4 to 6 weeks) (Lulich and Osborne, 1995) or if the infection represents a risk to the patient's health. Infection after recent urinary catheterization also should lead to culture collection.

Quantitative urine culture should be used to discriminate harmless bacterial contaminations (e.g., from the urethra) from pathogenic organisms. In a properly collected urine sample, bacterial counts of more than 10^5 are indicative of infection; counts between 10^3 and 10^5 organisms are considered suspect and should lead to a second culture. Samples collected by catheterization or midstream catch techniques are more likely to yield falsely positive cultures than are samples collected by cystocentesis, particularly in females. Thus, cystocentesis is preferred. Methods have been described for culture implementation in practice (Lulich and Osborne, 1995).

Escherichia coli is the predominant cause of UTIs in both dogs and cats (Barsanti, 1990; Lees, 1996a). Virulence factors for *E. coli* include increased adherence to uroepithelial cells, resistance to bactericidal activity, higher quantity of K antigen, presence of aerobactin, and hemolysin production (Sobel and Kaye, 1995). Among these, adherence appears to be the most important. *Staphylococcus* and other gram-positive organisms account for 25% of UTIs in dogs. Other causative agents include *Proteus, Klebsiella, Enterobacter,* and *Pseudomonas* (Barsanti, 1990). *Proteus* and *Staphylococcus* cause urinary alkalinization and as such often are associated with struvite formation in dogs. Organisms other than *E. coli* that cause UTIs in cats include *Proteus, Klebsiella, Pasteurella, Enterobacter, Pseudomonas,* and *Corynebacterium* (Lees, 1996a). *Mycoplasma* also should be considered as a less common cause of UTIs (Senior and Brown, 1996).

Antimicrobial Selection

Ideally, a drug that is renally excreted should be selected for treatment of UTIs. Urinary concentrations of such drugs often surpass serum concentrations (up to 300-fold), and as such susceptibility data should be based on urinary rather than plasma drug concentrations (Table 10–4). Indeed, drugs that might not be useful for treatment of non-UTIs (because of failure to achieve MIC in blood or tissues) often can be used to treat UTIs (e.g., carbenicillin, nitrofurantoin). In addition, renal elimination may result in bactericidal concentrations of drugs for which only bacteriostatic concentrations can be safely achieved in serum. Several caveats must be recognized, however, when basing antimicrobial selection on renal elimination and anticipation of high urine drug concentrations:

1. If the UTI is associated with infection in the blood

Table 10–4. Mean Urine Concentrations for Antimicrobials Used to Treat Urinary Tract Infections in Dogs

Drug	Dose	Route	Frequency	Mean Urine Drug Concentration (µg/mL)
Penicillins				
Penicillin G	37,000 U/kg	PO	8	295 ± 210
Penicillin	500 (7 mg/kg)	PO		100
Amoxicillin	11 mg/kg	PO	8	202 ± 93
	500 mg (7 mg/kg)	PO		500
Ampicillin	26 mg/kg	PO	8	309 ± 55
Indanyl carbenicillin	382 mg	PO		1000
	500 mg	PO		300
Cephalosporins				
Cefaclor	500 mg			900
Cefadroxil	500 mg	PO		1800
Cephalexin	500 mg	PO		1000
Cephradine	500 mg			1000
Aminoglycosides				
Gentamicin	2 mg/kg	SC	8	107 ± 33
Amikacin	5 mg/kg	SC	8	342 ± 143
Tobramycin	2.2 mg/kg	SC	8	66 ± 39
Fluorinated quinolones				
Enrofloxacin	5 mg/kg	PO	12	40 ± 10
Other				
Sulfisoxazole	1000 mg	PO		100
Trimethoprim	100 mg	PO		30–160
Trimethoprim/sulfadiazine	13 mg/kg	PO	12	55 ± 19
Nitrofurantoin	4.4 mg/kg	PO	8	100
	100 mg	PO		100
Nalidixic acid	1000 mg	PO		200
Tetracycline	18 mg/kg	PO	8	138 ± 65
	500 mg (7 mg/kg)			300
Chloramphenicol	33 mg/kg	PO	8	123 ± 40
Erythromycin	500 mg			30

Abbreviations: PO = orally; SC = subcutaneously.
*Assumes normal renal function.
Modified from Barsanti (1990).

(or in the presence of bacteremia), kidney, or prostate, then antimicrobial selection should be based on anticipated plasma (or tissue) drug concentrations and serum breakpoint MIC.

2. Exceptions may be made in the presence of decreased renal function. If renal function is sufficiently decreased, urinary drug concentrations also will be decreased. In addition, depending on the safety of the drug, drug doses may need to be decreased.

3. Many antimicrobials are characterized by a short elimination half-life. For renally eliminated drugs, however, plasma elimination half-life may not accurately reflect contact time of drug in the target tissue (i.e., urine). Presumably, drug eliminated in the urine will be in contact longer with the infected tissue (i.e., lower UTI) longer than other tissues, and therefore the basis for a recommendation to use drugs at a shorter interval when treating UTIs compared with other infections (Lulich and Osborne, 1995) may not be relevant for UTIs.

Caution is recommended when intervals shorter than 24 hours are used for aminoglycosides. Contact between drug and microbe in the urinary tract can be facilitated by administration of a drug immediately after micturition or before an anticipated micturition-free period (e.g., at night).

Empirical Therapy

Empirical therapy can be based on the most likely organisms to infect the UTI and their response to antimicrobials as shown by historical data collected in dogs and cats. Caution is recommended, however, because of the recent recognition of the growing incidence of antimicrobial resistance. Among the organisms frequently causing UTIs in dogs and cats, *E. coli, Proteus* species, *Pseudomonas aeruginosa,* and *Enterobacter* are among the organisms that vary widely in their susceptibility pattern and for which empirical therapy is more risky. For most infections, a number of antimicrobial drugs are appropriate, allowing cost and convenience to be the primary determining factors in drug selection for uncomplicated infections. An *uncomplicated infection* is one in which no underlying structural, neurologic, or functional abnormality can be identified (Lulich and Osborne, 1995). The absence of previous antimicrobial therapy should also be interpreted as uncomplicated. Once relapse occurs (see below), an infection should no longer be considered uncomplicated.

Uncomplicated infections caused by *E. coli* or *Enterobacter* are likely to respond to trimethoprim/sulfadiazine, a first-generation cephalosporin, or amoxicillin/clavulanic acid combination. *Klebsiella, Proteus,* and *Staphylococcus* are likely to respond to a first-generation cephalosporin or to amoxicillin/clavulanic acid. Amoxicillin or ampicillin is also likely to be effective for *Staphylococcus* or *Streptococcus.* It is the author's recommendation to base infection caused by *P. aeruginosa* on culture and susceptibility data whenever possible. Aminoglycosides (particularly amikacin) are likely to be effective. The fluorinated quinolones approved for use in veterinary medicine each are likely to be effective against any of the mentioned pathogens causing lower UTIs at concentrations achieved in urine. These drugs might better, however, be reserved for a second line of defense to minimize the advent of antimicrobial resistance. Note that MIC data for fluorinated quinolones are not likely to reflect concentrations achieved in urine, and many organisms that are noted as resistant may actually be susceptible in the urine. Fluorinated quinolones are also effective against *Mycoplasma* and *Ureaplasma.*

Attention should be paid to the pH of the urine compared with the pK_a of the chosen drug. In most situations, however, even if most of a drug is ionized (e.g., a weak base in an acidic environment), because drugs are concentrated in the urine, generally sufficient un-ionized drug is available to ensure effective concentrations. In the presence of an alkaline pH, weakly basic antibiotics might be considered (aminoglycosides, fluorinated quinolones). Because urease producers may alkalinize the urine, drugs including such organisms (e.g., *Proteus, Staphyloccocus,* and some *Klebsiella* species) should be selected. In the presence of an acidic urinary pH (perhaps caused by *E. coli*), weakly acid drugs (e.g., penicillins, cephalosporins, poentiated sulfonamides) might be better empirical selections.

Duration of Therapy

The duration for successful treatment of uncomplicated lower UTIs might be as short as 3 to 5 days (Lulich and Osborne, 1995). Treatment may need to be longer, however, if infection occurs anywhere other than the uroepithelium. In general, a 10- to 14-day therapeutic regimen is recommended for the first episode of therapy. The "test for cure" (Lulich and Osborne, 1995) can be based on a second culture 3 to 5 days into therapy. Cure should be anticipated only if the organism count is less than 100 per milliliter of urine. Urine culture a second time just before discontinuation of therapy has been recommended (Lulich and Osborne, 1995), particularly if antimicrobial prophylaxis is to be implemented. Although shorter term antimicrobial therapy (ranging from single high dose to dosing for 3 days) has proved effective for female human patients with a lower UTI, caution is recommended for use of this approach for dogs and cats. Drugs that have been used successfully by humans for short-term dosing include trimethoprim/sulfonamide combinations, aminoglycosides, selected cephalosporins, and fluorinated quinolones. Drugs that are metabolized to an active metabolite (e.g., enrofloxacin and ceftiofur) may be particularly conducive to single-dose therapy for animals, but these drugs apparently have not been scientifically studied for short-term use. Both single-dose and 3-day antimicrobial treatment regimens have been studied with dogs receiving amikacin and a trimethoprim/sulfonamide combination. Therapy was not uniformly successful, suggesting that caution should be used with this treatment regimen (Rogers et al., 1988). Factors that should preclude single-dose antimicrobial therapy for a lower UTI include recurrence, historical poor response to single-dose therapy, underlying predisposing factors to a UTI (including structural abnormalities of metabolic disorders such as diabetes mellitus, and hyperadrenocorticism), and either pyelonephritis or symptoms of a UTI that have occurred for more than 7 days.

For infections that reflect a relapse, the duration of therapy should be at least 2 weeks; however, for human patients suffering from a relapse, a higher cure rate occurred with a 6-week course of therapy. For animals, a duration of 4 to 6 weeks is recommended (Lulich and Osborne, 1995). Because relapse is likely to occur shortly after antimicrobial therapy is discontinued, cultures should be collected 7 to 10 days after cessation of therapy. The presence of relapse should lead to a longer course of therapy, perhaps at a higher dose. A new antibiotic should be selected if infection occurs more than 10 days after cessation of therapy (Lulich and Osborne, 1995); as more time elapses between cessation of therapy and the presence of bacteriuria, the more likely that reinfection is the cause of recurrence.

In the event of relapse after 6 weeks of therapy, 6 months of therapy or more may be necessary. A 3- to 6-month duration of therapy may be indicated for animals. Greater care should be taken, however, in the selection of antibiotics for longer term therapy, with special consideration to toxicity. Drugs that are used for long-term therapy for human patients include amoxicillin, cephalexin, trimethoprim/sulfonamide combination, or a fluorinated quinolone. Cultures should be repeated monthly, and, as long as significant bacteria are not present, the drug need not be changed. Should relapse occur after a drug is discontinued, the same drug or a new drug should be administered for a longer course of therapy. Long-term therapy may be particularly important for animals in which renal parenchymal damage is a risk.

Prophylaxis

Long-term prophylaxis can be implemented for patients at risk for recurrence. Prophylaxis (by definition) can occur only after the infection has been eradicated. The use of low doses of antimicrobials in the presence of bacteriuria is likely to lead to the generation of resistant organisms and is contraindicated. Thus, prophylactic antimicrobial therapy of UTIs is indicated for reinfection but not relapse (the latter suggests that the organism was never completely eradicated). The antimicrobial chosen for long-term prophylaxis should be both safe and inexpensive. Trimethoprim/sulfonamide combinations (monitor for immune-mediated reactions) and fluoroquinolones are examples. The dose generally can be reduced to 30% to 50% of the full dose (Lulich and Osborne, 1995).

Despite this low dose, therapeutic concentrations of drugs are likely to be achieved in urine; in addition, subtherapeutic concentrations of drugs often are sufficiently inhibitory to prevent infection of the uroepithelium. The drug should be administered at night to maximize contact of the drug with the urinary tract. Intermittent urine cultures (monthly) are indicated to detect breakthrough infections in animals receiving long-term antimicrobial prophylaxis. Negative cultures for 6 to 9 months or more may indicate that prophylaxis is no longer necessary.

Adjuvant Therapy

Diuresis has been advocated in the treatment of UTIs in humans. Advantages include rapid dilution of bacteria, removal of infected urine, and subsequent rapid reduction of bacterial counts. In patients with pyelonephritis, an added advantage may be enhanced host defenses: Medullary hypertonicity inhibits leukocyte migration, and high ammonia concentration inactivates complement. In the presence of vesiculoureteral reflux, however, diuresis may increase the risk of acute urinary retention.

Use of drugs to modify urinary pH may facilitate the antibacterial effects of urine. The presence of ionizable organic acids (hippuric and β-hydroxybutyric acid) in an acidic pH may enhance the antibacterial activity of the urine. Antibacterial activity may be increased by ingestion of cranberry juice (if urinary pH is acidic), which contains precursors of hippuric acid. Methenamine releases formaldehyde at a urinary pH of 5.5 or less, which also can increase antibacterial activity of urine. Methenamine has, however, been associated with methemoglobinemia in the cat. In human patients, urinary acidification is very difficult to achieve and can result in dissolution of crystals. Urinary acidification is recommended rarely and only with concomitant use of organic acids (or methenamine).

Local urinary analgesics, such as phenazopyridine, rarely are indicated for the management of urinary tract infections. Dysuria is most likely to respond to appropriate antimicrobial therapy. These drugs cause methemoglobinemia in cats.

Drugs or nutraceutical products that enhance polysulfated glycosaminoglycan synthesis (e.g., ADEQUAN, pentosan polysulfate, glucosamine, chondroitin sulfate) might be considered for patients with complicated UTI. Such materials may cover or help repair the uroepithelium, thus decreasing bacterial adherence.

Pyelonephritis

Treatment for pyelonephritis may require hospitalization. Oral antibiotic therapy is acceptable for mild to moderate cases as long as oral therapy is tolerated well. Because renal dysfunction can be life threatening, antimicrobial selection should ultimately be based on culture and susceptibility data. Therapy can be initiated empirically; however, resistance among *E. coli* organisms should lead to selections other than amoxicillin and ampicillin. Trimethoprim/sulfonamide combinations, amoxicillin/clavulanic acid combinations, cephalosporins, and fluorinated quinolones remain good choices for human patients (Sobel and Kaye, 1995). Pyelonephritis can be associated with bacteremia, particularly gram negative. Clinical signs indicative of severe, life-threatening infection should lead to parenteral antibiotic therapy with predictably effective drugs (e.g., aminoglycosides, fluorinated quinolones, extended spectrum β-lactams, and third-generation cephalosporins). Combination therapy also should be strongly considered. The high concentration of antibiotic that facilitates treatment of the lower urinary tract (bladder and lower) may not occur in pyelonephritis; thus attention must be closely paid to using sufficiently high doses and frequent dosing. Drugs whose efficacy is dependent on a hypotonic environment (compared with the target organism) such as β-lactams may be less effective in the face of medullary hypertonicity. As with infection lower in the tract, bacterial numbers should decrease dramatically within the first 48 hours. For uncomplicated pyelonephritis, 14 days of therapy may be sufficient. Cultures should be repeated as previously indicated during and within 1 to 2 weeks of discontinuation of therapy. Complications such as abscessation may require surgical intervention and longer term therapy.

Prostatitis

Pathophysiology

Bacterial prostatitis can present as either an acute or chronic infection. One does not necessarily lead or follow the other. Among the causes of prostatic infection, ascending infection and urine reflux appear to be most likely. Acute prostatitis often is accompanied by fever, pain, and symptoms typical of a UTI. Palpation of the prostate reveals tenderness, swelling, and (potentially) a fluctuant surface. Care should be taken when palpating the prostate so that the risk of bacteremia is minimized. Chronic bacterial prostatitis most commonly is caused by gram-negative coliforms, with *E. coli* being most common, followed by *Klebsiella, Enterobacter, Proteus mirabilis,* and *S. aureus.*

Antimicrobial Selection and Use

Antimicrobial penetration into the noninflamed canine prostate is limited. Drugs that are basic and lipid soluble appear to diffuse through tissues best, including macrolides (e.g., erythromycin and presumably azithromycin and clarithromycin); fluorinated quinolones, and trimethoprim/sulfonamide combinations. The intense inflammatory response that accompanies acute prostatitis facilitates antimicrobial movement into the prostate (Sobel and Kaye, 1995), although high doses should be used to ensure adequate concentrations at the site of infection. Parenteral antibiotics should be used in the presence of life-threatening infection; otherwise, oral therapy is acceptable. Duration of therapy should be at least 4 weeks to minimize the risk of progression to chronic prostatitis. Prostatic abscessation generally requires surgical intervention. Chronic prostatitis in human patients is difficult to cure unless infected tissue is surgically excised. Chronic prostatitis generally results in relapse. Therapy when successful generally requires 1 to 2 months of therapy. Antimicrobials that penetrate the noninflamed prostate (e.g., fluorinated quinolones, trimethoprim/sulfonamide combinations, or macrolides) should be selected (Sobel and Kaye, 1995).

Adjuvant therapy for the treatment of prostatitis includes stool softeners and, if indicated, analgesics. Neutering should be considered.

INFECTIONS OF THE UTERUS

Endometritis

Endometritis is associated with sanguineous or purulent vaginal discharge in either the pregnant bitch (if the cervix is open) or nonpregnant bitch (Wallace, 1995). As with many organ systems, organisms causing uterine infections tend to be members of the normal flora of the reproductive tract. Organisms most commonly associated with uterine infections include *Streptococcus* species, *E. coli, Salmonella, Campylobacter, Mycoplasma,* and *Chlamydia* (Wallace, 1995). Bacterial infections of the uterus resulting in endometritis can be responsible for infertility, abortion, stillbirths, and fetal death. Treatment of endometritis differs in the presence of pregnancy (live fetuses) in part because of potential injury to developing fetuses. Regardless of the antimicrobial, any type of placentation is sufficiently intimate to allow movement of drug administered to the dam or queen to cross the placenta and enter the fetus. In general, however, the fetus can excrete water-soluble drugs more easily than lipid-soluble drugs because water-soluble drugs can be eliminated in the allantoic fluid. In contrast, drug-metabolizing enzymes of the fetal liver are immature and essentially nonfunctional. Although metabolizing activity increases as the term of pregnancy ends, activity remains sufficiently weak that drug elimination is probably ineffectual. Thus, lipid-soluble drugs tend to remain in the fetus. When possible, drugs that are water-soluble should be selected for treatment of infections in the pregnant bitch.

The β-lactams are preferred with amoxicillin combined with clavulanic acid or a cephalosporin as first choice, assuming the target organism is included in the spectrum. Culture and susceptibility data should be the basis for antimicrobial selection for treatment of endometritis, even if antibiotics are begun before results are received. Should susceptibility data indicate β-lactams as resistant, aminoglycosides can be used. Pediatric (and presumably fetal) canine kidneys are protected from aminoglycoside damage because the cortical regions do not fully develop until several weeks postpartum. Fluorinated quinolones also appear to be safe for the developing fetus, although the risk of cartilage damage even in the developing fetus might lead to an alternative class of drugs. Response to antimicrobial therapy is indicated by resolution of vaginal discharge, which should occur within several days of beginning therapy. Therapy should continue for 2 to 3 weeks (Wallace, 1995). In the case of fetal death, prostaglandin therapy may be indicated in order to evacuate the uterus (see chapter on reproductive therapy). Evidence of septicemia indicates more dramatic and aggressive therapy (see later).

Pyometra

Although bacterial infection is secondary to the cystic changes associated with pyometra, the infection is the primary cause of illness and death. Organisms most commonly associated with pyometra include *E. coli* (the majority of infections), hemolytic *Streptococcus, Staphylococcus, Klebsiella, Pasteurella, Pseudomonas, Proteus,* and *Moraxella* (Johnson, 1995). Wadas et al. (1996) demonstrated that *E. coli* associated with pyometra in dogs was derived from fecal flora and were also identical to those simultaneously cultured from the urine. Host and microbial factors (see Chapter 8) play a large role in the pathogenesis of pyometra and response to drug therapy. In addition to the obvious impact of inflammatory and other debris on antimicrobial efficacy, the local immune response of the uterus is impaired (Johnson, 1995). Complications such as bacterial peritonitis and endotoxin contribute to mortality. Endotoxin concentrations generally are increased before implementation of drug therapy, further complicating antimicrobial selection (Johnson, 1995).

Antimicrobials that minimize endotoxin release (e.g., imipenem, selected third-generation cephalosporins, aminoglycosides, and fluorinated quinolones) should be considered for pyometra. Response to endotoxemia should be anticipated in patients with pyometra, and antimicrobial treatment should be aggressive. Therapy for pyometra should include supportive measures such as fluid rehydration and, if indicated, therapy for endotoxic shock. Glucocorticoid therapy should be avoided (see Chapter 17). Surgical removal of the infected uterus is the treatment of choice; however, antimicrobial therapy should be implemented regardless of whether ovariohysterectomy is performed. Prostaglandin therapy may be implemented in selected cases (see chapter on reproductive therapy).

Culture and susceptibility data should be collected before empirical therapy with a bactericidal drug that includes *E. coli* in its spectrum is begun. Although a β-lactam antibiotic is generally an excellent first choice, concern with rapid cell death and release of lethal quantities of endotoxin should lead to (1) selection of imipenem, the β-lactam associated with the least endotoxin release; (2) combination therapy with a non-β-lactam antibiotic (e.g., an aminoglycoside or fluorinated quinolone) that is administered before (1 to 2 hours) the β-lactam; or (3) slow administration of the β-lactam, perhaps over the course of 1 hour. Administration of an antiendotoxin-binding agent, such as polymyxin B (in doses much lower than those necessary for a bactericidal effect), might also be considered, although the use of such drugs has not been studied for their endotoxin-binding safety and efficacy in small animals.

DERMATOLOGIC INFECTIONS

Pyoderma

Microbial Flora

The microflora of the skin is composed of both resident and transient organisms. Resident organisms in the skin of dogs include *Micrococcus*, α-hemolytic streptococci, aerobic diphtheroids, *Propionibacterium acnes* and *Staphylococcus* species. *Pseudomonas, Proteus*, and *Corynebacterium* have also been cultured from normal dogs. Among the organisms cultured from the skin of normal dogs, only *Staphylococcus intermedius* is a likely cause of pyoderma. *Staphylococcus aureus* and other *Staphylococcus* species are much rarer causes of superficial pyodermas in dogs (Ihrke, 1996a, b; Lloyd, 1996). *Staphylococcus intermedius* is involved in approximately 90% of canine pyodermas (Ihrke, 1990, 1996a, b). The resident status of *S. intermedius* in the skin is debatable. Although cultured frequently from either the skin or hair of normal dogs, *S. intermedius* may simply be a contaminant or a transient organism, acting as a "nomad," proliferating only when environmental circumstances are supportive of growth (DeBoer, 1994). The microflora of dogs with pyoderma differs from the microflora of the skin in normal dogs. Even skin not clinically affected by pyoderma is characterized by increased staphylococcal colonization (Ihrke, 1996a, b). Eventually, *Staphylococcus* becomes the predominant organism in the skin. It can change the local environment, allowing proliferation of other organisms. Thus, even when disease has progressed to the point that gram-negative infections (e.g., *E. coli, Proteus*, and *Pseudomonas*) (Ihrke, 1996a, b) are involved (generally deep pyodermas), *S. intermedius* is likely to be involved. In fact, if *S. intermedius* is not cultured from the skin lesion, the laboratory or culture technique should be questioned (Ihrke, 1990). When pyoderma is treated, concomitant infection with *S. intermedius* should be assumed, and control of infection by *S. intermedius* in such cases should facilitate treatment of other organisms, including gram-negative ones.

Diagnostic aids can be useful to discriminate infection from colonization in the skin. Gram staining and cytology are particularly helpful. The presence of rods is indicative of a mixed infection (with gram-negative organisms); intracellular organisms indicate phagocytosis and thus infection rather than colonization. Cytology may help stage or identify the cause of disease: Mononuclear infiltrations indicate deep, chronic infections; large numbers of *Staphylococcus* species in pustules may be indicative of hyperadrenocorticism (Ihrke, 1996a, b).

Predisposing Factors

Because of its nature, pyoderma should be expected to be complex and difficult to treat. Pyoderma is defined as a bacterial infection in skin associated with pus, and both the organ (skin) and local environment (pus) present barriers to drug movement and efficacy (Ihrke, 1990). The location of the infection in the skin also confounds therapy (Ihrke, 1996a, b). The depth of the infection (surface to cellulitis) in particular can have a negative impact on successful drug therapy. Unchecked disease can spread from the skin surface (e.g., intertrigo), which is a location generally amenable to topical antimicrobial therapy, to the superficial skin structures (e.g., impetigo, superficial folliculitis), which is less responsive. As the infection becomes more deeply seated, systemic antimicrobial therapy becomes more important (Fig. 10–2) (Ihrke, 1990, 1996a, b). Lesions of deep pyoderma begin in the distal portion of the

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Figure 10–2. Histologic section of deep pyoderma. Scarring and accumulation of inflammatory debris present both mechanical and functional barriers to drug penetration. (Photograph courtesy of Bayer Animal Health.)

hair follicle, often extend below the follicle, and may be accompanied by furunculosis and a granulomatous response. As the disease worsens, antimicrobial therapy becomes more difficult (Ihrke, 1990, 1996a, b). Cellulitis is the most severe manifestation of pyoderma and involves infection of the dermis and adjacent subcutaneous tissues. Although uncommon, infection at this depth can become life threatening if sepsis develops. Obviously, one of the goals of therapy for pyoderma is to prevent the progression of clinical signs.

Not all pyodermas are difficult to treat; indeed, most will respond to initial antibiotic therapy. For some patients that initially respond to antimicrobial therapy, however, recrudescence of their disease will occur after therapy is discontinued. The most likely cause for recrudescence is failure or inability to control underlying skin diseases that predispose the skin to persistent or recurrent infections. Examples include ectoparasitism, seborrhea (cornification disorders), allergies (atopic dermatitis, flea or food allergies), and endocrinopathies (hyperadrenocorticism or hypothyroidism) (Ihrke, 1990, 1996a, b). Anatomic abnormalities such as skin folds (intertrigo) also predispose the patient to bacterial infection (Ihrke, 1990, 1996a, b). These underlying factors must be corrected when possible. In many patients, however, correction of the underlying cause is not possible. In addition, other factors complicate treatment of pyoderma. These include the effects of the infecting microbe, mechanical and physiologic barriers presented by the normal animal, functional and structural sequelae of disease, and limitations of the drugs. The interaction among these factors is difficult to predict. Their impact can, however, be largely minimized by decision making during antimicrobial selection that is based on the interactions.

Materials released from microbes facilitate invasion, impair cellular phagocytosis, and damage host tissues. Most staphylococci associated with canine pyoderma produce "slime," a material that facilitates bacterial adhesion to cells. Soluble mediators released by organisms (hemolysin, epidermolytic toxin, leukocidin) may damage host tissues or alter host response (Ihrke, 1996a, b). Staphylococcal organisms contain protein A, which impairs antibody response, activates complement, and causes chemotaxis (Cox et al., 1986). Selected *Staphylococcus* species suppress or avoid intracellular killing once phagocytized by leukocytes (Tulkens, 1990). Viability of the organisms will be maintained inside the phagocyte, allowing not only survival but perhaps also continued replication inside the cell. Subsequent release of the organism upon the death of the phagocyte allows reinfection, leading to persistent or recurrent infections.

The surface of the skin normally presents several barriers to bacterial invasion and colonization. Cells of the stratum corneum desquamate from the surface of the skin and hair follicles, and the lipid-rich environment between the cells impedes bacterial movement (Ihrke, 1996a, b). Epithelial proliferation follows injury to the skin, decreasing the likelihood of bacterial invasion. Sebum and sweat contain antibacterial chemicals such as inorganic salts (Ihrke, 1996a, b) and lipids (White, 1996). Finally, resident microflora help keep invading microflora "in check." Differences in the incidence and ease of treatment of pyoderma in dogs versus cats and other species may reflect anatomic and physiologic differences in their skin (Ihrke, 1996a, b). Canine skin may be predisposed to pyoderma because the stratum corneum is thin, compact, and contains less lipid material. As such, canine stratum corneum may present a less efficient barrier to bacterial invasion compared to other species. Canine hair follicles lack a lipid-squamous "plug," which may facilitate bacterial penetration into the hair follicle (Ihrke, 1996a, b; Lloyd, 1996). Finally, the pH of canine skin is higher than that of other species, perhaps providing an environment more conducive to bacterial proliferation (Ihrke, 1996a, b).

Skin also has a well-developed immune response, composed of proteins, immunoglobulins located in the basement membrane, cells of the immune system located in the dermis and epidermis, and regional lymphoid tissue (Ihrke, 1996a, b). Under normal circumstances, components of bacteria that penetrate the skin stimulate a humoral response (immunoglobulins G and M) which in turn activates effector mechanisms leading to an acute inflammatory response (Ihrke, 1996a, b). Phagocytic white blood cells (initially neutrophils) that respond to inflammatory mediators use a number of oxidative (e.g., myeloperoxidase) and nonoxidative (e.g., bactericidal permeability increasing protein) mechanisms to kill phagocytized invading bacteria (Aucoin, 1996). Unfortunately, host responses to bacterial invasion may become deleterious and can negatively impact successful therapy.

Pathophysiology

The inflammatory response may facilitate bacterial penetration, is responsible for clinical signs associated with the disease, and may preclude antimicrobial penetration of the skin. Cutaneous mast cells triggered by antistaphylococcal immunoglobulin E may increase epidermal permeability and facilitate bacteria or bacterial antigen penetration in patients with allergic skin disease (Ihrke, 1996a, b; White, 1996). Some staphylococcal organisms release "super antigens" (enterotoxin), which may cause interleukin release and an inappropriately large T-lymphocyte response in the skin (Ihrke, 1996a, b; White, 1996; Morales et al., 1994). The severe and persistent inflammatory response leads to pruritus, and self-trauma further aggravates bacterial penetration. The disease may develop an autoimmune component (Ihrke, 1996a, b). These long-term changes, in conjunction with inflammatory disease, predispose the patient to recurrent pyoderma.

As bacterial skin disease progresses, pathologic changes become barriers to drug distribution to the site of infection. The barriers vary with the site of infection, ranging from very superficial structures (epidermal and hair follicle) to deep structures below the hair follicle. Hair follicles may rupture, leading to furunculosis. Granulomatous changes and keratinaceous debris may act as a foreign body, perpetuating the inflammatory response (Ihrke, 1996a, b). These deeper structures may become isolated by fibrous tissue as disease progresses unchecked. Foci of organisms located in these isolated beds are a likely cause of recurrent infections with deep pyoderma (see Fig. 10–2), as can intracellular survival of phagocytized organisms (see Figs. 8–13 and 8–14) (Ihrke, 1996a, b).

Considerations in Drug Selection

For most antimicrobials used to treat canine pyoderma, side effects become less important to the selection and other considerations can take precedence. Exceptions might occur for erythromycin; up to 50% of animals should be expected to develop gastrointestinal "upset" when treated with erythromycin (Kunkle et al., 1995). Immune-mediated side effects caused by potentiated sulfonamides may limit their long-term use (Cribb et al., 1996). Although there have been no documented reports of sulfonamide toxicity caused by sulfonamide/ormetoprim combinations, it is likely that toxicity will occur for any sulfonamide component. Sulfonamides are also able to decrease thyroid hormone synthesis. Marked decreases in circulating thyroid hormones have been documented in dogs receiving 30 mg/kg of a potentiated sulfonamide twice daily. Thyroid function should return to normal once the drug is discontinued.

Drug Movement to the Site of Infection

Distribution of antibiotics applied topically is limited by the presence of the stratum corneum, although distribution presumably will be enhanced in the presence of inflammation. Accumulation of inflammatory debris, however, also impedes drug movement after either topical or systemic administration. Shampooing not only moves inflammatory debris but also softens the stratum corneum, thus facilitating movement of topically applied antimicrobials to deeper tissues. Distribution of systemically administered antibiotics to the skin is somewhat limited even with normal conditions. Despite the skin being the largest organ of the body, blood flow to the skin represents only 9% of the cardiac output. Drug distribution to the skin takes longer than to tissues with greater blood flow. Although skin is well perfused, blood supply to the epidermis consists of capillaries that lie under the epidermis, and drugs must passively diffuse to the epidermis and, with folliculitis, through the hair follicle. The plexi of arteries and veins that supply the skin include arteriovenous anastomoses that allow blood to bypass capillary beds. Blood supply to the skin can be altered easily in disease, particularly in the extremities and deep dermis.

Most antibiotics used to treat pyoderma are lipid soluble, although the degree varies with each drug. Drugs that are characterized by a favorable distribution pattern to the skin include the fluorinated quinolones, the sulfonamides (including those "potentiated"), the macrolides (erythromycin), the lincosamides (clindamycin and lincomycin); and chloramphenicol (Neu, 1994).

Antimicrobial Resistance

Antimicrobial resistance may impact antimicrobial therapy of pyoderma. *Staphylococcus aureus,* the causative organism of human pyoderma, has developed a forbidding pattern of resistance toward many antimicrobials. In contrast, *S. intermedius* has not been as adaptable: Comparison of data collected during the last two decades suggests that susceptibility patterns of the organism have not changed dramatically (Ihrke, 1996a, b). Yet, although *S. intermedius* is a species distinct from *S. aureus,* transmission between these organisms of plasmids responsible for multiple antimicrobial resistance may be a factor that might ultimately contribute to antimicrobial failure in canine pyoderma (Ihrke, 1996a, b). The prudent clinician will take a proactive approach to avoiding the development of antimicrobial resistance among organisms that cause canine pyoderma. Previous antibiotic use should be considered in the selection of an antimicrobial without the benefit of culture and susceptibility data. The impact of previous antibiotic use on the susceptibility pattern of a microbe to other drugs is controversial (Ihrke, 1996a, b). Susceptibility of *Staphylococcus* to penicillins, tetracyclines, and potentiated sulfonamides may, however, be decreased after use of antibiotics. Susceptibility data should be considered as a basis for selection of antimicrobials for patients with a history of recent antimicrobial use. Certainly, drugs previously used and that have subsequently failed should be avoided. Resistance may more likely be encountered in gram-negative organisms associated with deep pyoderma (Ihrke, 1996a, b), and culture and susceptibility data become increasingly important for antimicrobial selection with these infections. Resistance is more likely to develop with long-term therapy (as must occur for deep pyoderma) and conditions that are likely to result in subtherapeutic concentrations at the site of infection. Repetitive cultures that yield increasing MICs for the same drug may indicate development of resistance, and alternative drugs or combination antimicrobial therapy should be considered in such cases (Neu, 1994).

The combination of clavulanic acid with amoxicillin "protects" amoxicillin from β-lactamase destruction; as such, the combination, rather than amoxicillin alone, should be used when treating pyoderma (Bush et al., 1989). Narrow-spectrum semisynthetic penicillins (dicloxacillin, cloxacillin, and oxacillin) are resistant to β-lactamases. Cephalosporins are commonly used as first choice antibiotic therapy for treatment of canine pyoderma because they are less likely than penicillins to be destroyed by β-lactamases produced by *Staphylococcus* species (Caprile, 1988). β-Lactamase resistance can also be avoided by using alternative (non-β-lactam) antimicrobials. Other mechanisms of bacterial resistance may, however, develop to any antimicrobial, particularly if the resistance is plasmid mediated. Fluorinated quinolones (enrofloxacin) might be considered for long-term therapy in part because plasmid-mediated resistance has not yet been clinically demonstrated for these drugs (Neu, 1989; Power et al., 1992; Witte and Grimm, 1991). Avoidance of subtherapeutic concentrations is paramount to antimicrobial success, and concentrations can be minimized if dosing regimens take into account the effects of host factors at the tissue site.

Antimicrobial Selection

Selection of the Most Appropriate Drug

The number of antibiotics recommended for initial therapy of pyoderma is proportional to the number of papers published regarding therapy. Clinician preferences vary, and appropriately so, with experience. Although clinicians might not agree on their first choice antimicrobial, however, there is little disagreement regarding the target organism. Initial therapy should begin with an orally bioavailable drug effective against *S. intermedius*. Ideally, the dosing interval should be 12 hours or longer to facilitate owner compliance. Subsequent considerations regarding drug selection vary with the severity of the disease. The more severe the disease, the greater the care that must be taken with antibiotic selection. Tissue penetration should be increasingly predictable as the infection deepens. Detection and avoidance of resistance become increasingly important as the duration of therapy and the risk of subtherapeutic drug concentrations at the site of infection increase. With few exceptions, adverse effects are not a common cause of therapeutic failure and, as such, may not have a major impact on antimicrobial selection. Cost often has a major impact on selection. Client money can just as easily, however, be spent on prolonged therapy with an inappropriate drug (or dosing regimen) as it can be on an appropriate drug (and dosing regimen).

A number of drugs are indicated for initial therapy of pyoderma. Despite the relative susceptibility of *S. intermedius* to β-lactam antibiotics, β-lactamase resistance may be a concern. Hence, a non-β-lactam drug might be selected particularly for infections complicated by recurrence or previous antimicrobial therapy. Appropriate drugs include potentiated sulfonamides (i.e., trimethoprim or ormetoprim sulfonamide combinations), erythromycin, and lincomycin (clindamycin and lincomycin perhaps being too expensive). Increasingly common reports of immune-mediated diseases such as keratitis sicca or impaired thyroid hormone secretion may decrease the use of potentiated sulfonamides, particularly at high doses and for long-term therapy. An advantage might, however, be once a day therapy (sulfadimethoxine/ormetoprim), which has proved effective for some authors (Ihrke, 1996a, b). Chloramphenicol may also be an effective first choice antibiotic, although concerns for human exposure to the drug may preclude its use.

Alternatively, many clinicians choose a β-lactam antibiotic that tends to be more resistant to *Staphylococcus* β-lactamases. Examples include amoxicillin/clavulanic acid and a first-generation cephalosporin such as cephalexin or cefadroxil. These three antibiotics tend to be equal in efficacy but differ in cost, with cephalexin probably being the most cost effective. Amoxicillin/clavulanic acid may, however, be less likely to induce resistant bacteria at subinhibitory concentrations (Ihrke, 1996a, b). Alternatively, β-lactamase-resistant β-lactams such as oxacillin and dicloxacillin can be used for initial or long-term therapy, although expense may preclude their selection until initial therapy fails.

For infections that do not respond to initial therapy and become increasingly complicated, a drug that targets both *S. intermedius* and gram-negative organisms should be selected. Because bactericidal concentrations at the site of infection are desirable (Lloyd, 1996), a drug that is likely to distribute to and through the inflammatory site is desirable. The use of β-lactams should be reconsidered for infections associated with marked inflammatory debris or scarring because these drugs do not penetrate these barriers well (Neu, 1994). The fluorinated quinolones, such as enrofloxacin or marbofloxacin, are the drugs of choice for complicated infections. They are characterized by rapid bactericidal activity, and their spectrum includes both *S. intermedius* and gram-negative organisms (Lloyd, 1996; Ihrke, 1996a, b). Absorption from the gastrointestinal tract is excellent after oral administration, and the drug distributes very well to the skin (Vancutsem et al., 1990). Inflammatory debris and fibrous tissue should be traversed well with little impact on antimicrobial efficacy (Vancutsem et al., 1990). Efficacy of the fluorinated quinolones is maintained despite slow growth of organisms or low oxygen tension (Wetzstein, 1994). Enrofloxacin and marbofloxacin are accumulated in white blood cells (Tulkens, 1990; Caprile, 1988; Hawkins et al., 1998) and is able to penetrate the lipopolysaccharide covering of gram-negative organisms. Enrofloxacin is characterized by the lack of plasmid-mediated resistance to DNA gyrase in clinical patients (although resistance may be conferred that decreases antimicrobial penetration due to changes in porin size). The drug is effective against most *Pseudomonas*, although increasing resistance to this organism and to *S. aureus* has been seen in humans (Power et al., 1992; Witte and Grimm, 1991) and in some veterinary practices. The use of fluorinated quinolones other than those approved for veterinary use is discouraged for dogs and cats. Compared with enrofloxacin, both ciprofloxacin and norfloxacin are characterized by poorer oral bioavailability (60% or less for ciprofloxacin and even less for norfloxacin). Although the dose of these drugs might be increased to compensate for differences in absorption, the unpredictability of peak concentrations is disconcerting for a drug whose efficacy depends on peak concentrations. In addition, ciprofloxacin (which often is reported in lieu of enrofloxacin in laboratories using human testing kits) is equipotent to enrofloxacin for most organisms. Finally, enrofloxacin is metabolized in the liver to ciprofloxacin in both dogs and cats, thus contributing further to the antimicrobial efficacy (Kung et al., 1993).

The use of aminoglycosides for treatment of complicated pyoderma should be limited to life-threatening conditions associated with sepsis (e.g., cellulitis) or to organisms with known (i.e., based on susceptibility data) resistance to enrofloxacin. The aminoglycosides are generally effective against *Staphylococcus* species and gram-negative organisms including *Pseudomonas* (Neu, 1994). Resistance is less likely, however, to develop against amikacin compared with gentamicin, particularly for *Pseudomonas* species. The aminoglycosides do not distribute well through inflammatory debris and fibrous tissue, are not effective against facultative aerobes (i.e., in the presence of reduced oxygen tension), and they are not accumulated in white blood cells (Tulkens, 1990). Hence, care must be taken to ensure that an adequate dose is given. Once daily administration is encouraged and combination antimicrobial therapy with a β-lactam effective against the target organism should be strongly considered.

Designing a Dosing Regimen

Perhaps the most important, yet often overlooked, reason that bacterial pyoderma is difficult to resolve in dogs is use of an inappropriate dosing regimen of an otherwise appropriate drug. Although the importance of culture and susceptibility testing for chronic, recurrent, and deep pyoderma cannot be denied, it is critical to realize that the in vitro conditions do not and cannot mimic the microenvironment of the host. They also do not reflect the ability of the drug to reach the site of infection, including inside white blood cells. The effects of underlying skin disease including changes in the patient's immune status (local or systemic) also cannot be taken into account by the in vitro system. Thus it is critical that both the dose and interval of a dosing regimen be designed such that drug concentrations are maximized at the site of infection.

In general, the dose of an antibiotic should be as great as possible when treating complicated pyoderma in order to ensure effective concentrations at the site of infection. Twice the recommended dose has been suggested by some authors, and this is a reasonable starting point (Ihrke, 1996a, b). Doses up to fourfold higher than recommended may be necessary for organisms whose MIC for the drug is close to breakpoint or in the presence of factors that will decrease the movement or efficacy of antibiotic at the site of infection. Higher doses are critical for concentration-dependent drugs. The greater the inflammatory response at the site, and the deeper the infection, the more important the need for increasing the dose. If necessary, selection of an antibiotic might be made with an emphasis on safety so that doses can be increased with minimal risk of side effects. High tissue concentrations in relation to the MIC of the infecting organism are particularly important to the antimicrobial efficacy of selected drugs, most notably the aminoglycosides and the fluorinated quinolones. For aminoglycosides (and apparently fluorinated quinolones), antimicrobial efficacy is enhanced in the presence of a high inhibitory quotient in part because of an enhanced postantibiotic effect. In addition, both aminoglycoside efficacy and safety are facilitated by a moderately long drug-free period during a dosing interval. Thus, for aminoglycosides, once daily administration of the total daily recommended dose should be considered for pyoderma. With the fluorinated quinolones, the dose should be likewise modified to maximize plasma (and thus tissue) drug concentration; this is particularly important for organisms whose MIC approaches the breakpoint for enrofloxacin (≥4 μg/mL). Once daily dosing with enrofloxacin at a high dose (10 mg/kg) may ultimately become the generally recognized regimen for this drug for complicated pyoderma.

The interval of drug administration is equally or more important than the peak drug concentration for other antimicrobials, most notably the β-lactams and "bacteriostatic" antibiotics. For these drugs, the duration that the drug concentration at the site is above the MIC is more important to antimicrobial efficacy. Thus, for β-lactams, antimicrobial efficacy is likely to be more facilitated by a shorter dosing interval than by increasing the dose. For example, to improve the efficacy of amoxicillin/clavulanic acid, an 8-hour dosing interval should be used in lieu of 12-hour intervals when treating problematic cases. Unfortunately, owner compliance is less likely with this regimen and may be a reason for considering an alternative class of drugs for treatment of complicated pyodermas.

The route of drug administration might be considered for complicated pyoderma, particularly that which is life threatening. The oral route of drug administration is obviously most convenient, but several factors can minimize peak concentrations of antimicrobials in the plasma and thus tissue. Food impacts the oral bioavailability of some drugs. Because of this (and other reasons) ampicillin and tetracyclines are not particularly good choices for treatment of pyoderma. Although fluorinated quinolones are 100% bioavailable, the rate of their absorption can be slowed by food that may decrease peak plasma concentrations. Intravenous administration of any antibiotic available in IV form should be used for life-threatening infections or for conditions for which peak tissue concentrations must be maximized. This difference may be important when dealing with an organism with a high MIC.

Duration of Therapy

An insufficient duration of therapy is another common cause of therapeutic failure in the treatment of pyoderma with an otherwise appropriate antibiotic. Recommendations vary with authors, although the consensus is that the duration of therapy for pyoderma increases with the severity of infection (Ihrke, 1996a, b). Ideally, therapy should extend 7 to 21 days (depending on the severity of infection) after surface healing has occurred. Superficial infections should resolve within 3 to 4 weeks of antimicrobial therapy if the patient is immunologically normal. Deep pyoderma or the presence of immune compromise requires at least 4 to 6 weeks of therapy. Treatment for 12 weeks or longer is not unusual. Evaluation by the clinician at 14-day intervals may be prudent, and reculture should be considered for infections for which resistance is a concern. Clinical evaluation should continue for several more weeks after therapy has been discontinued to ensure resolution.

Several authors have suggested alternative dosing regimens for antibiotics for patients whose disease will not resolve. These alternative dosing regimens include dosing once daily, every other day, or pulse dosing. Pulse dosing involves administration of a drug using full dosing regimens either 2 days a week or every other week. With the every-other-week approach, if recurrence is prevented, the duration of the "off" week can be gradually increased. Intervals of greater than 3 weeks are, however, likely to result in recrudescence (Ihrke, 1996a, b). Conceivably, the risk of resistance should be increased if infecting microorganisms are exposed to intermittent concentrations of drugs. Clinically, however, this does not appear to happen. Two possible reasons can be offered. First, the impact of prolonged antimicrobial therapy on normal skin microflora might be minimized by pulse dosing. Second, pulse dosing at high (full) doses may be less likely to facilitate resistance than lower doses on a continuous basis. Ensuring that concentrations of drug at the site of infection are not subtherapeutic during the on weeks may minimize the risk of resistance. Compliance may be an issue with pulse dosing, and care must be taken to ensure that drug therapy is maintained.

Adjuvant Therapy

The importance of adjuvant therapy should not be overlooked in the treatment of pyoderma (Ihrke, 1996a, b). Adjuvant therapy may target the underlying skin disease or support antimicrobial therapy. Antihistamines and 3-omega fatty acids should be considered when appropriate in conjunction with antimicrobial therapy to control the inflammatory response associated with infection or the underlying disease. Antimicrobial efficacy will be complicated by coadministration of drugs that alter the immune response. Most notably, glucocorticoids should be avoided for patients with pyoderma. Although these drugs effectively ameliorate the inflammatory response and are useful in cases of pruritus leading to self-trauma, they also may facilitate the spread of bacterial infection (Ihrke, 1996a, b). Other adjuvant therapies to be considered include immunomodulatory therapy and topical antimicrobial therapy. Although immunomodulatory therapy (levamisole and cimetidine) may prove beneficial, there is often a bimodal effect with these drugs: if the proper dose is not given, immunosuppression rather enhancement of the immune system may occur (Ihrke, 1996a, b).

Topical antimicrobial therapy can have a notable beneficial impact on successful systemic antimicrobial therapy. Topical antimicrobial therapy may be the only method of antimicrobial administration needed to treat surface and some superficial pyodermas. Topical antimicrobial therapy should be used as an adjuvant for superficial and deep pyodermas. Shampoos are preferred because they remove debris that might impede drug movement or impact drug efficacy. In addition, the combined effect of a topical and systemic antimicrobial may result in additive or synergistic antibacterial effects. Although irritating with long-term use, products that contain benzoyl peroxide tend to be the most efficacious in controlling bacterial growth and removing accumulated debris on the skin (Kwochka and Kowalski, 1991). Products containing chlorhexidine, sulfur, triclosan and ethyl lactate are also acceptable. Shampoos should be used twice weekly (Ihrke, 1996a, b).

Miscellaneous Infections

Dapsone is an antibiotic that inhibits para-aminobenzoic acid metabolism to folic acid. Selected mycobacterial strains, most notably *Mycobacteria leprae* or *M. lepraemurium*, are exquisitively sensitive to its effects. In addition, the drug appears to be capable of some form of immunomodulation and may prove beneficial in deep skin infections associated with a pyogranulomatous response for which no organism has been identified. Because of difficulty associated with identifying infectious organisms such as *Nocardia* species and atypical mycobacterial organisms, however, use of dapsone should be reserved until a susceptible organism has been identified or other causes of inflammatory skin disease have been ruled out. The drug has not been studied in animals, and in humans it is characterized by marked differences in disposition. Hemolytic episodes have been reported in humans; however, generally these individuals are suffering from metabolic defects of red blood cells. Dapsone also is used to treat bites caused by brown recluse spiders in humans. When administered within 48 hours of the bite, tissue necrosis is markedly decreased and wound healing is subsequently faster.

OTITIS EXTERNA

Pathophysiology

Inflammation of the ear canal and the proximal pinna affects up to 20% of dogs, whereas fewer (up to 6% of) cats are affected (Royschuk and Luttgen, 1995). A number of causes can be identified in otitis externa, and their resolution is paramount to successful therapy. These include foreign bodies, allergies, parasites (e.g., mites or chiggers), skin disorders of a keratinization or sebaceous origin, or an autoimmune disorder. Structural characteristics of the ear also can predispose the animal to otitis externa, including pendulous ears, higher number of ceruminous glands, the vertical and horizontal paths of the canal, hair in the ear canal, stenotic ear canals, or neoplasm. Environmental factors also can contribute to the difficulty in treating otitis externa, including external conditions that perpetuate excessive moisture (such as humidity and bathing) or heat or irritants (irritating medicaments or shampoos). The presence of yeast or bacteria that are part of the normal flora perpetuate the inflammatory process, and, with time, the inflammatory process itself will cause proliferative changes that complicate therapy. One of the more important predisposing factors to otitis externa is inappropriate treatment, including undertreatment and overtreatment (Royschuk and Luttgen, 1995).

Bacterial organisms found in normal ears include *S. epidermis* and *S. intermedius* and *Micrococcus* species. Coliforms are found only occasionally. Infection usually can be discriminated from colonization by the presence of large numbers of organisms. Infection also is indicated by the presence of inflammation and phagocytized bacteria. Inflammation reflects, in part, the breakdown of fatty materials by organisms into irritating by-products. *Staphylococcus intermedius* is the most common organism (30% to 50%) associated with otitis externa, followed by *P. aeruginosa, Proteus* species, *Streptococcus* species, *E. coli,* and *Corynebacterium* species. The infecting organism also appears to be time dependent in that acute otitis is generally associated with *Staphylococcus* whereas chronic otitis more commonly involves *Pseudomonas*. In cats, *Pasteurella multocida* joins *Staphylococcus* and *Streptococcus* as commonly infecting organisms; the coliforms and *Pseudomonas* are less common causes. *Malassezia pachydermatis* is an opportunistic yeast that occurs in up to 49% of normal dogs and 23% of normal cats. The numbers increase in dogs with otitis, however, being present in 80% or more of dogs. Although it is likely that *Malassezia* contributes to otitis externa, its role is not clear.

Antimicrobial and Adjuvant Options

Because successful treatment of otitis externa is critically dependent on proper cleaning, it is difficult to separate antimicrobial therapy from adjuvant therapy. The goals of therapy are to identify and resolve the primary factors, reduce inflammation, and control or eradicate infection. Sedation or anesthesia may be necessary for proper cleansing. Cleansing should remove irritating oils, waxes, and other debris that might serve as a nidus of infection by providing a microenvironment favorable to the growth of microorganisms. Ear cleaning should be less aggressive in the presence of severely swollen or proliferative canals; in such patients, initial therapy might begin with anti-inflammatory doses of glucocorticoids and antibiotics, both systemically and topically.

Ceruminolytics contain various surface active agents or emulsifiers (dioctyl sodium sulfosuccinate, carbamide peroxide, squalene, propylene glycol, glycerin, oil) that dissolve wax accumulation and associated debris should be used as an initial flush. Less "messy" water-soluble agents (dioctyl sodium sulfosuccinate, propylene glycol) are often preferred (Royschuk, 1994).

Carbamide peroxide, a common ingredient of human preparations but seldom found in veterinary medicine, releases nascent oxygen, causing a bubbling action that softens and removes debris. Combination products may contain drying agents such as isopropyl alcohol, silicone dioxide, and alpha-hydroxy acids (lactic, malic, or salicylic acid). In addition to their drying effects, these materials may also have mild antimicrobial effects (Royschuk, 1994). Flushing solutions facilitate removal of debris. Although water and saline are the safest, some products contain germicidal products. Chlorhexidine can be diluted to a 0.05% solution and used topically. Although ototoxicity should lead to cautious use in the presence of a perforated eardrum, one study failed to provide evidence of damage after 21 days of therapy in dogs with experimentally traumatized membranes (Royschuk, 1994). Povidone-iodine at 0.1% to 1.0% can provide bactericidal activity in flushing solutions, although it can cause contact irritation. Because of ototoxicity, solutions less than 0.5% are preferred if the eardrum is ruptured. Iodine might also be administered as a polyhydroxidine complex (Xenodine). It contains 0.5% of titratable iodine and as such is less irritating and provides a longer duration of activity. Efficacy against *Pseudomonas* has been established with this product. It must be used in an aqueous environment and as such should be used within 2 hours after cleaning to maximize its effects (Royschuk, 1994). Acetic acid is a relatively inexpensive agent, available as white or brown vinegar in a 5% solution. Antimicrobial effects occur because of direct damage as well as acidification of the local environment. The acidic pH may also facilitate removal of necrotic debris. *Pseudomonas* succumbs to a 2% solution within 1 minute of contact (Royschuk, 1994) whereas a 5% solution is effective against *Staphylococcus, Streptococcus, E. coli,* and *Proteus.* The preparation is irritating at 2% to 5% concentrations, however, and inhibition of wound healing and ototoxicity may occur at concentrations of 2.5%. Dilutions of 1:1, 1:2, or 1:3 in water daily to every other day have been recommended.

Topical products intended for treatment of otitis externa (Tables 10–5 and 10–6) generally contain various drugs intended to target bacteria, yeast, and inflammation. Antibacterial agents often include products that are associated with severe systemic toxicity when given orally or parenterally; topical administration generally is safe. Ototoxicity is, however, likely for many antimicrobial drugs when administered in the ear canal, especially in the presence of a perforated tympanic membrane. Caution is recommended when any medicament is used in the presence of a perforated eardrum.

Examples of antibiotics used in otic preparations include the aminoglycosides gentamicin (0.3%), tobramycin (0.3%), and neomycin (0.33%) and the cell membrane active agents colistin (0.3%) and polymyxin B (5000 IU/mL). Silver sulfadiazine (0.5%) is an ointment approved for humans for prevention or treatment of infection in burn patients. Its spectrum includes *Pseudomonas* species and

Table 10–5. Examples of Commercially Available Topical Products Used for Treatment of Otitis Externa

	Active Ingredient			
Product	***Antibacterial***	***Antifungal***	***Anti-inflammatory***	**Vehicle/Other Ingredients**
Cortisporin Otic*	Polymyxin B Neomycin		Hydrocortisone 1%	
Coly-Mycin*†	Colistin 0.3% Neomycin		Hydrocortisone 1%	Polysorbate 80, acetic acid, sodium acetate
Derma 4‡	Neomycin 0.25%	Nystatin	Triamcinolone acetonide 0.1%	Polyethylene, mineral oil, gel (ointment)
Forte-Topical‡	Neomycin 0.25% Polymyxin Procaine penicillin G		Hydrocortisone acetate 0.2% Hydrocortisone sodium succinate 0.125%	Suspension
Gentocin otic	Gentamicin 0.3%		Betamethasone valerate 0.1%	Hydroxycellulose, glacial acetic acid, water, ethanol, alcohol, glycerin, propylene glycol
Liquichlor‡	Chloramphenicol		Prednisolone 0.17%	Mineral oil, petrolatum (ointment), squalane, tetracaine 0.42%
Neo-predef‡	Neomycin 0.35%		Isoflupredone acetate 0.1%	Anhydrous lanolin, petrolatum, mineral oil (ointment)
Otic solution*	Polymyxin B Neomycin		Hydrocortisone 1%	
Otomax†	Gentamicin 0.3%	Clotrimazole	Betamethasone valerate 0.1%	Ointment
Panolog‡	Neomycin	Nystatin	Triamcinolone acetonide 0.1%	Polyethylene, mineral oil, gel (ointment)
Tobrex ophthalmic*	Tobramycin 0.3%			
Tresaderm‡	Neomycin 0.32%	Thiabendazole	Dexamethasone 0.1%	Glycerin, propylene glycol, water, alcohol

*Human preparation.
†Second-line product.
‡First-line product.

Table 10–6. Home-Made Otic Products or Modifications of Commercially Available Otic Products

Drug	Antimicrobial	Anti-inflammatory	Modification
Baytril	Enrofloxacin 22.7 mg/mL	None	Dilute 1 : 1 up to 1 : 25 in water, 5% DMSO, saline, Synotic
Novalsan solution	Chlorhexidine diacetate 2%	None	Dilute 1 : 1 in water
Silvadene	Silver sulfadiazine 0.5%	None	Mix 1 : 1 with water
SYNOTIC	Enrofloxacin* 22.7 mg/mL	Fluocinolone acetonide	Replace 1 mL of Synotic solution with 1 mL of injectable preparation
Tris-EDTA	Tris-EDTA	None	6.05 mg EDTA, 12 g tromethamine (Trizma base), 1 L distilled water. pH must be adjusted to 8 with hydrochloric acid.† Autoclave
Xenodine	Polyhydroxidine 1%	None	Dilute 1 : 5 with water

*Represents a modification.

†Addition of 0.3 g GENTOCIN/L has been recommended (Royschuk, 1994); see text for precautions.

as such might be considered as a "last ditch" medicament for refractory cases of otitis externa. The product may, however, cause skin irritation. Antifungal agents generally target *M. pachydermatis* and include the imidazoles clotrimazole (1%), miconazole (1%), and thiabendazole (1%) and the polyene macrolides nystatin and amphotericin B. Among these, those containing thiabendazole might be considered first line (Royschuk, 1994; Royschuk and Luttgen, 1995). Anti-inflammatories often are included in topical otic solutions. Examples include dimethylsulfoxide (60%), and glucocorticoids. Among the glucocorticoids included in otic preparations, fluocinolone (0.01%) may be the most potent (Royschuk, 1994), followed by betamethasone, dexamethasone, isoflupredone, triamcinolone, and prednisolone.

Dimethylsulfoxide also is included in some otic preparations as a vehicle. The agent is very hygroscopic and as such is an effective carrier agent for other drugs included in an otic preparation. In addition, dimethylsulfoxide provides mild antibacterial and antifungal actions. Other vehicles used to administer drugs useful for otic disorders include solutions, lotions, ointments, and other oil-based products. Occlusive oils may be undesirable for exudative lesions. Ointments and oil-based products can, however, be used in cases of chronic otitis externa that are dry. Generally, topical preparations should be applied twice daily.

A number of "home-made" remedies have been recommended for treatment of otitis externa (see Table 10–6). For example, Tris-EDTA (ethylenediaminetetraacetic acid) is a topically applied buffer that contains a chelating agent (EDTA) that removes calcium and magnesium ions from the lipopolysaccharide covering of gram-negative organisms and the cell wall of gram-negative and gram-positive organisms. Penetration of antibacterials subsequently is facilitated. Treatment should be timed such that microorganisms are exposed to Tris-EDTA before peak concentrations of antibiotics reach the site of infection. Direct addition of antibiotics such as gentamicin to the buffer solution is less desirable than pretreatment with Tris-EDTA, followed later by antibiotics. Drug interactions may decrease the efficacy of the aminoglycoside. In addition, maximum efficacy of the two antibiotics may require sufficient time for Tris-EDTA to act on the cell wall. Tris-EDTA should be considered in combination with other topical or systemic antimicrobials.

Caution is recommended when making new preparations or modifying old preparations. A number of drug interactions between drugs and their vehicles can inhibit the efficacy of any of the drugs. In addition, drugs must be dissolved in order to be effective, and the addition of solid drugs (i.e., as powders or crushed tablets) to ointment vehicles (e.g., petrolatum jelly) is likely to yield an occlusive but minimally effective agent. Some acceptable modifications of commercially available products are noted in Table 10–6.

Systemic therapy is indicated for severe infections. Glucocorticoids may be necessary for rapid control of inflammation regardless of the cause or duration of infection. General principles of glucocorticoid therapy should be followed (see Chapter 17). Likewise, systemic antibiotics may be indicated in combination with topical therapy. No data support selection of the same versus different, but complementary, antibiotics when both topical and systemic therapy are used. The advantage of using the same antibiotic topically as administered systemically is increased likelihood of effective drug concentrations at the site of infection. The advantages of combination therapy have been discussed previously (see Chapter 8) and are particularly appealing for the treatment of chronic, minimally responsive otitis externa. The risk of insufficient concentration of either drug should, however, lead the clinician to maximize the dose of either drug. Oral antifungals, such as ketoconazole or itraconazole may be indicated for control of infection caused by *Malassezia*.

Treatment of Specific Causes of Otitis Externa

Chronic Otitis

Resolution of chronic or recurring otitis includes treatment of specific diseases of the ear that allow perpetuation of infection or inflammation. Culture and susceptibility data collected during cleansing of the ears under general anesthesia should be the basis of antimicrobial selection. Thorough visual examination accompanied by cytologic examination can help identify other underlying causes.

Acute Otitis Externa

Although ultimately the ear must be clean and dry, severe swelling or proliferation indicates less aggressive therapy initially and the potential need for glucocorticoid therapy (topical or systemic). Once swelling is decreased, cleaning will be more effective. If the tympanic membrane is intact, initial cleaning begins with an application of a ceruminolytic, which can then be rinsed with water, or an antimicrobial solution such as chlorhexidine, povidone or polyhydroxidine iodine, or acetic acid. If the tympanic membrane is ruptured, only water or saline should be used for cleansing because many of the cleansing agents are ototoxic. Cleansing can be accomplished at home, although initial cleaning might be more thorough if performed under general anesthesia, particularly in intractable patients. For ears in which a large amount of debris has accumulated, removal of material may require alligator forceps through an otoscope and flushing with either an open-ended tomcat catheter or a 3.5 to 5 French feeding tube and syringe or an in-house vacuum system. Hair that might obstruct drainage of the ear canal or facilitate collection of debris should be removed.

Because otitis externa tends to be associated with the same pathogens, regardless of the underlying cause, topical medication applied after cleaning generally contains an antibiotic, antifungal, and glucocorticoid. Glucocorticoids decrease not only swelling and proliferation but also apocrine and sebaceous secretions. Note that topical administration does not preclude suppression of the hypothalamic-pituitary-adrenal axis, and the long-term use of these products should be avoided. In the event of moderate to marked swelling of the ear canal and pinna, a short term of systemic glucocorticoids may be indicated. To minimize the risk of antibiotic resistance, products that contain commonly used "first-line" antibiotics and antifungals directed toward *Malassezia* might be chosen for acute (nonrecurring) otitis externa. Culture and susceptibility data are the best basis for selection of the most appropriate second-line antibiotic. In the event of moderate swelling of the ear canal and pinna, topical antibiotic therapy probably should be accompanied by systemic therapy. Therapy for acute otitis externa should be followed through rechecks at 10- to 14-day intervals. Resolution generally requires 2 to 4 weeks.

Bacterial Otitis

The need for antimicrobial therapy for bacterial otitis externa should be based on an increased number of bacterial organisms. The presence of inflammatory debris and intracellular organisms supports bacterial infection. A "first-line" product containing neomycin or chloramphenicol might be appropriate. Severe inflammation may indicate the need for systemic antibiotic therapy. Among the more commonly selected systemic antibiotics are amoxicillin/clavulanic acid, a fluorinated quinolone, or a first-generation cephalosporin (Royschuk, 1994). Failure to respond to "first-line" medicaments may indicate the need for culture. Some authors recommend discontinuing antimicrobial therapy for 3 to 5 days before culture; however, the presence of bacteria in the face of antibiotics should lead to growth regardless of the presence of antibiotics. Otic preparations containing gentamicin or tobramycin might represent the second line of medicaments for infections resistant to neomycin or chloramphenicol.

Otitis caused by *Pseudomonas* can be among the more frustrating syndromes to treat and often is the incentive behind the formation of home-made otic products. Flushing with an acetic acid–based solution is indicated. Commercially available otic products have been modified by the addition of drugs effective against *P. aeruginosa* (amikacin, enrofloxacin, polymyxin B, or colistin sulfate) or the addition of anti-inflammatory drugs. Several alternatives can be considered for refractory cases. Enrofloxacin has been added to commercially available otic solutions, but it also is the oral antibiotic of choice. The maximum end of the dosing regimen should be considered when treating a refractory case of *Pseudomonas*-induced otitis externa (i.e., 20 mg/kg once daily). Other products to be used in resistant cases include silver sulfadiazine, Xenodine, and chlorhexidine (1.5%).

Malassezia pachydermatis

Malassezia pachydermatis is an opportunistic organism that, in large numbers, causes proliferatory changes in the ear. Its presence may contribute to bacterial otitis, and thus its control may be important to the treatment of otitis. Because control of inflammation may be paramount to controlling infection by *Malassezia,* glucocorticoids such as those provided in otic preparations may be indicated. Ketoconazole appears to be among the most efficacious, followed by miconazole, nystatin, clotrimazole, and amphotericin B (Royschuk, 1994). Thiabendazole (the active antifungal in TRESADERM), however, may be sufficiently effective, allowing other antifungals to be reserved for resistant cases. Routinely used cleaning and drying solutions should be used on a daily to alternate-day basis to facilitate control.

Ear mites generally occur in young animals, and their presence is determined by direct examination. Carbaryl and pyrethrin-based products should be used for at least a 3-week cycle to ensure killing of adults and immature mites. Products containing thiabendazole should be selected because the product probably kills all stages of mites, including eggs. Polyhydroxidine iodine may also be effective when administered once weekly for 4 weeks. *Otodectes* can be treated with ivermectin given orally once a week for 4 weeks or subcutaneously every 10 to 14 days. With severe infestations, ivermectin should be combined with other topical miticides. Because other portions of the body may harbor mites that infest the ear, affected animals should be dipped.

Seborrheic otitis or ceruminous otitis usually accompanies endocrinopathies. Secondary bacterial and *Malassezia* infections are not uncommon with this disorder. The first-line medications should be effective for management of most cases, but longer term management may require a combination of cleansing/drying/glucocorticoid products applied one to three times weekly. Cocker spaniels and other breeds occasionally develop what appears to be a local hypersensitivity to cerumen, resulting in a progressively inflammatory, proliferative disease that ultimately may result in calcification of auricular cartilages. Control of inflammation initially may require oral glucocorticoids accompanied by topical application of a potent (e.g., dexamethasone or fluocinolone) glucocorticoid. Topical antimicrobials (antibacterial and antifungal) probably are also indicated; systemic antibiotic therapy may also be necessary. The ears should be frequently flushed with cleansing and drying agents. For some animals, long-term, low-dose glucocorticoid therapy may be necessary.

Swimmer's ear generally occurs because frequent swimming encourages low-grade inflammation and subsequent maceration. Ears should be kept clean and dry. Topical anti-inflammatory therapy may be necessary and, in some cases, topical antimicrobial therapy. Products should be used on the day of swimming and for several days after.

INFECTIONS OF THE GASTROINTESTINAL TRACT

Oral Cavity

Use of culture and susceptibility data as a basis for antimicrobial selection in the mouth is complicated by normal polymicrobial anaerobic growth. Culture of a relatively pure growth may indicate the organism as the cause of infection. Representative cultures should be obtained from infections in deeper, isolated tissues (such as abscessation or osteomyelitis). Care should be taken in collection of the anaerobes; these organisms can be exquisitely sensitive to oxygen. Because infections are likely to involve anaerobic organisms, drugs that target anaerobes and distribute well to the mucosa and, if indicated, bone, should be selected. Examples include clindamycin, the aminopenicillins, including amoxicillin/clavulanic acid combinations, and metronidazole. Among these drugs, clindamycin has proved the most effective in penetrating the glycocalyx and other material serving as a barrier to antimicrobial penetration in the presence of plaque. Metronidazole-fluorinated quinolone combinations (e.g., ciprofloxacin [humans] or enrofloxacin) have been shown to act synergistically in the treatment of peridontitis. Anaerobic organisms, including *Bacteroides* species, produce β-lactamases and as such clavulanic acid combinations should be considered for more complicated or serious infections. The role of gram-negative organisms in causing infections should not be ignored even in the presence of abscessation.

Prophylactic antibiotic use is commonplace for dental procedures but not warranted for healthy animals (West-Hyde and Floyd, 1995). The duration of antibiotic therapy before the procedure depends on the intent of prophylaxis. Protection of the patient predisposed to endocarditis during the procedure is particularly important. A single dose of antibiotics timed such that peak plasma concentrations occur as the dental procedure is begun may be sufficient for most animals. For an orally administered drug, the time of administration should approximate the time to peak tissue concentrations, which is generally 1 to 2 hours after administration. For intravenously administered drugs, drug concentrations will not be highest at the tissue site until distribution has occurred, generally 30 to 60 minutes after administration. If the intent of prophylactic therapy is to decrease the bacterial load of the oral cavity before the procedure, then the drug should be administered several days before the procedure. Because the oral cavity contains a large population of normal organisms, prophylaxis for surgical procedures involving the oral cavity often has been extended to a week or longer before or after the procedure. A novel drug delivery system has recently been designed for treatment of periodontal disease in dogs. Doxycycline, characterized by a broad antimicrobial spectrum, is prepared in a vehicle that is injected into the periodontal pocket after dentistry. The moist environment causes the vehicle to gel, resulting in a slow-release drug delivery system. In clinical trials associated with Food and Drug Administration approval, animals receiving the drug after dental work improved more rapidly than animals treated with a placebo. The cleaning procedure itself, however, appeared to be the more important means of improving the health of the local environment.

Antiseptic agents can prove beneficial in home care dentistry (West-Hyde and Floyd, 1995). Chlorhexidine is considered one of the most efficacious products and is indicated for patients with periodontal disease. It is available in several 12% preparations: an oral acetate rinse (Novaldent, Fort Dodge); a more palatable gluconate solution (CHX Oral Cleansing Solution, VR$_x$ Products), or a gluconate gel. In addition to having an immediate bactericidal effect, chlorhexidine adsorbs to the tooth pellicle, which serves as a reservoir, allowing continuous release of chlorhexidine. Chlorhexidine has caused toxicity when applied as a disinfectant in catteries following grooming by the cats. Although there are no reports of chlorhexidine toxicity when used for periodontal disease in cats, research has focused primarily in beagle dogs, and caution may be indicated when this product is used for cats. Fluoride-containing products should be used cautiously because dogs appear to be more susceptible than other species to acute toxicosis.

Esophagus Through Small Intestine

Primary infections of the upper gastrointestinal tract are unusual. Thus, treatment of infections generally includes resolution of the underlying cause (Twedt, 1995).

Megaesophagus

Regardless of the cause of megaesophagus, aspiration pneumonia is a serious, potentially life-threatening complication. The continuous use of antibiotics for prevention of pneumonia in cases of unresolvable megaesophagus is controversial and probably not indicated unless continuous bacterial infection has been documented. The inflammatory response of aspiration pneumonia is likely to be induced by chemicals (including hydrochloric acid) or foreign bodies. The treatment of pneumonia was discussed earlier.

Stomach

Vomiting originates from many central and peripheral causes, including acute gastritis. Acute gastritis, in turn, has many causes and is most likely to respond when the underlying cause is resolved, which generally occurs in 1 to 5 days. Bacteria as a cause of vomiting are unlikely, and antimicrobial therapy rarely is indicated. Therapy is supportive, including fluids and appropriate additives (e.g., potassium if vomiting is profuse) and antiemetics.

The normal flora of the stomach of dogs consists of large spiral bacteria, including *Helicobacter* species (Willard, 1995). Spiral bacterial and a nonpathogenic chlamydial organism occur in the feline stomach. The role of spiral organisms (most notably *Helicobacter* species) in gastrointestinal diseases in dogs and cats is currently being investigated, but it is likely that these organisms will become the target of drug therapy in the medical management of several diseases. Numbers of bacteria in the gastrointestinal tract gradually increase distally to the ileocecal valve (Greene, 1990). Numbers of bacteria abnormally increase when normal bowel defenses are impaired. Several mechanisms exist to protect the normal gastrointestinal tract from infection. Among the most important are gastric and bile acids, which limit the concentration of bacteria. In humans, over 99.9% of ingested coliform bacteria are killed at a pH of less than 4 within 30 minutes. In contrast, no reduction of bacteria occurs in the stomach in the presence of achlorhydria (Guerrant, 1995). Among the reasons that *Helicobacter pylori* has been recognized for its pathogenicity in the cause of human gastrointestinal disorders is its ability to alter the gastrointestinal pH and thus increase host susceptibility to other infections (Guerrant, 1995). Drugs that contribute to bacterial overgrowth include antisecretory drugs and antacids. Mucus and mucosal tissue integrity provide physical barriers and help clear bacteria from the upper and small bowel (Guerrant, 1995).

Small and Large Intestines

Normal Control Mechanisms

Intestinal Motility

Intestinal motility has several roles in the prevention of gastrointestinal bacterial infection. Gastrointestinal motility and diarrhea help removed offending pathogens from the gastrointestinal tract, not unlike the cough reflex does in the respiratory tract. Bowel stasis increases the risk of bacterial overgrowth in the small intestine and the added risk of inflammatory bowel disease. Antimotility drugs (e.g., opioids) increase the risk of overgrowth (Guerrant, 1995); in contrast, the use of prokinetic drugs may be beneficial if decreased motility is a factor in the development of diarrhea. Obstruction or stasis of intestinal or bile flow and decreased mucosal blood flow contribute to bacterial infections in the intestinal tract (Greene, 1990).

Normal Microflora

Microflora is established at 2 to 3 weeks of life. The population remains stable under normal conditions but does vary among species. The high-meat diet of carnivores supports a predominant population of streptococci and *Clostridium perfringens* while suppressing *Lactobacillus* (Greene, 1990). Anaerobes comprise the majority of intestinal microflora, outnumbering aerobic organisms by 10-fold to 1000-fold (Greene, 1990); in humans, 99.9% of enteric microbes are anaerobic. Aerobic gram-negative coliforms in humans include *E. coli, Klebsiella, Proteus,* and enterococci (Guerrant, 1995). The normal microflora is important to the control of infecting microorganisms in the gastrointestinal tract. Normal floral bacteria compete for available nutrients, maintain redox potentials, and produce antibacterial compounds that prevent colonization by infecting organisms. Normal flora also have a number of physiologic functions. Microflora produce volatile fatty acids and vitamins as well as metabolize bile acids and some drugs. Indigenous (anaerobic) microbes attach to the intestinal epithelial surface and act synergistically with host immune mechanisms to interfere with experimental *Salmonella* infections (Guerrant, 1995). Gram-negative aerobes such as *Proteus, Enterobacter,* and *E. coli* act in concert with host immune mechanisms to prevent infection with *Vibrio* species.

In the presence of diarrhea, anaerobic numbers decline because the organisms require stasis and a low oxygen potential. In the presence of antimicrobials, the loss of normal microflora in humans can shift the balance of bacteria to gram-negative aerobes and replacement of anaerobes with organisms such as *Pseudomonas, Klebsiella,* anaerobes such as *Clostridium,* and yeast (*Candida*) (Guerrant, 1995). Diarrhea associated with antibiotic use has long been associated with disruption in the balance of normal microflora in part due to the loss of toxic products produced by normal microflora. The number of organisms (e.g., *Salmonella*) needed to cause infection is markedly reduced after administration of a single dose of selected antibiotics (e.g., for *Salmonella,* streptomycin). Resistance to infection can be restored with a return of the normal enteric flora (in humans, especially *Bacteroides*). Outbreaks of gastrointestinal infections in people, particularly with *Salmonella,* can be associated with antimicrobial exposure (Guerrant, 1995).

Host Immunity

Host intestinal immunity plays an important role in the prevention of gastrointestinal infection. The intestine is normally in a state of physiologic inflammation due to the presence of neutrophils, macrophages, plasma cells, and lymphocytes. The loss of neutrophils and their phagocytic capability results in an increased susceptibility to gram-negative (rod) infections originating in the gastrointestinal tract (Guerrant, 1995). Secretory IgA is resistant to intraluminal degradation and as such provides an important source of local immune protection. The intestinal antibodies are directed toward a variety of bacterial antigens, including endotoxin, capsular material, and exotoxins. In addition, they may have bactericidal, opsonic, or neutralizing effects on bacteria (Guerrant, 1995). In the nursing animal, several compounds produced by the mother are important. In humans, breast milk contains lactoferrin, lysosome, phagocytic activity, oligosaccharide fractions, and other materials that afford protection to the newborn.

Factors Facilitating Infection

A number of microbial factors facilitate gastrointestinal infection. Factors that determine bacterial virulence and pathogenicity are well represented by *E. coli* and include production of enterotoxins; the capacity to invade; induction of hemorrhagic colitis; and expression of adherence and enteroaggregation (Guerrant, 1995). Production of enterotoxins (defined as having a direct effect on intestinal mucosa such that fluid secretion increases) by organisms such as *Staphylococcus, C. perfringens, Bacteroides,* and *E. coli*) can result in disruption of fluid fluxes across the intestinal mucosa. The organisms producing enterotoxins generally are part of the normal microflora but, in the presence of predisposing factors (e.g., garbage enteritis, bacterial stasis, bacterial overgrowth), proliferate in the small intestine. Noninvasive organisms can induce diarrhea by actions of exotoxins that stimulate adenyl cyclase and subsequently sodium, chloride, and water secretion into the intestinal lumen. Cytotoxins produced by several pathogens cause mucosal destruction and a subsequent inflammatory response (Greene, 1990; Guerrant, 1995). Some organisms (*Salmonella*, particularly in the ileum; and *Shigella*) are capable of causing mucosal invasion, resulting in hemorrhagic feces. Enterohemorrhagic *E. coli* produces cytotoxins, and the enterotoxin produced by *Clostridium perfringens* also causes cytotoxicity. The pathogenesis of *Campylobacter jejuni* and *Helicobacter pylori* infections also has been attributed to cytotoxins (Guerrant, 1995).

Adherence factors contribute to the ability of organisms to colonize the intestinal epithelium and cause infection. Adherence antigens generally are fimbrial in nature but are distinct from those responsible for urinary adherence. A number of distinctly different adhesins have been described for enteric microorganisms. Invasiveness as represented by *Shigella* and selected strains of *E. coli* results in the destruction of epithelial cells and superficial inflammation. The degree of invasiveness depends on the protein to which the organism is bound and may also depend on the production of cytotoxic exotoxins (Guerrant, 1995). Newer antimicrobial agents may target the adherence of toxins, acting to prevent their synthesis or antagonizing their effects and thus blocking the ability of the microbe to infect. Drugs also may minimize the actions of enterotoxins. Other virulence factors that facilitate infection in the gastrointestinal tract include motility, chemotaxis, and production of mucinase (Guerrant, 1995). The ability of *H. pylori* to alter gastric acidity has already been mentioned.

Treatment of Bacterial Diarrhea

The role of bacteria in causing diarrhea and the treatment of these causative organisms also is discussed in Chapter 27. Several diarrheal syndromes have been described in small animals (Greene, 1990). Neonatal colibacillosis occurs in dogs and cats. Puppies are generally only a week old, but diarrhea can persist in older puppies. Factors contributing to infection with *E. coli* include immunologic incompetency (including failure of passive transfer), immaturity of intestinal epithelial cells (nonselectively permeable) for the first 2 to 3 days of life, and exposure to *E. coli* in colostrum. The syndrome of bacterial overgrowth is a cause of chronic or recurrent diarrhea; German shepherds appear to be predisposed. Increased numbers (more than 10^5/mL) of *E. coli* and enterococci (considered normal flora) and selected anaerobes (e.g., *Clostridium* species) are increased in duodenal secretions of affected dogs. Underlying factors are not well described but include motility disorders, hypochlorhydria, and deficiency of secretory antibody (IgA). Animals generally respond to antimicrobial therapy.

Adjuvant Therapy

The importance of fluid therapy for patients with diarrhea induced by bacterial infections should not be overlooked. The composition of electrolyte losses in severe diarrhea is similar to that of serum, and both IV and oral rehydration therapy should reflect this composition. Absorption of oral solutions depends on the intact intestinal mucosa. Sodium and glucose should be present in equimolar concentrations; amino acids (e.g., glycine) might be added in veterinary preparations to facilitate electrolyte absorption (Greene, 1990). In humans, an oral recipe is recommended to contain 3.5 g NaCl, 2.5 g $NaHCO_3$, 1.5 g KCl, and 20 g glucose (dextrose) per liter of boiled water (Guerrant, 1995).

INFECTIONS ASSOCIATED WITH BACTEREMIA

Infective Bacterial Endocarditis

Causative organisms of infectious endocarditis (IE) are not limited to bacteria but include *Chlamydia, Mycoplasma,* fungi, and viruses. Because more is known about bacteremia caused by bacteria, it serves as the basis of discussion here. Regardless of the type of infecting organisms, the events that allow development of IE are probably the same. Infective endocarditis includes infection and colonization of the endocardial and adjacent surfaces of the cardiac valves, their supportive structures, and the wall of the heart. The incidence in dogs and cats appears to be low (0.06% to 6.6% based on necropsy findings) (O'Grady, 1995).

The incubation period of IE—the time between the bacteremic event and the onset of clinical symptoms—may be up to 2 weeks. Historically, IE has been classified in humans based on the progression of untreated disease. Acute disease is characterized by a fulminant course of events, characterized by high fever, evidence of systemic involvement, leukocytosis, and death generally within a couple of days (taking as long as several weeks). Subacute (death in 6 to 12 weeks) and chronic (greater than 12 weeks) IE are characterized by a slower course characterized by low-grade fever and vague clinical signs (Sheld and Sande, 1995).

Pathophysiology

Microbial Factors

Several independent events lead to the development of IE (Sheld and Sande, 1995). The endothelial surface of the valve first must be altered (e.g., by blood turbulence induced by valvular insufficiency) such that bacteria can adhere to and colonize it. Initially, the damaged surface induces the deposition of platelets and fibrin, forming a nonbacterial thrombotic endocarditis. Organisms with the ability to adhere to platelets or fibrin have the advantage of inducing disease with a smaller inoculum. Bacterial adhesion to the thrombus forming on the damaged valvular surface is critical to the initial stages of IE. The thrombus provides a protective environment for bacterial growth in that phagocytic and other host defenses are impaired below the surface (Sheld and Sande, 1995). This thrombus provides a surface for bacterial adherence and colonization. Organisms particularly capable of adherence include *S. aureus, S. epidermis,* and *P. aeruginosa.* Colonization is followed rapidly by the formation of a protective sheath of fibrin and platelets, which facilitates bacterial multiplication and vegetative growth. Transient bacteremia such as might occur during dental, gastrointestinal, or urogenital procedures can lead to colonization of a thrombus that has formed on a previously damaged valve. Infecting organisms tend to be "nonpathogenic" organisms associated with the mucosal surface (e.g., *Propionibacterium acnes, Actinomyces, S. epidermidis*) or organisms that are resistant to complement-mediated bactericidal activity (e.g., *E. coli, P. aeruginosa, Serratia marcescens*). Within genera of bacteria, differences in the ability of strains to cause infection also might be related to their lack of encapsulation (thus allowing adherence). Dextran, a complex polysaccharide produced by some organisms (e.g., *Streptococcus*) is an example of an extracellular molecule that may facilitate bacterial adhesion to the valvular surface. Some organisms are able to directly bind to endothelial surfaces; indeed, endothelial cells may initially ingest some organisms (e.g., *S. auerus*) as the initial event. Some organisms are potent stimulators of platelet aggregation (e.g., *Staphylococcus* and *Streptococcus* species), thus facilitating growth of the vegetative lesion as well as formation of thrombi in systemic circulation (Sheld and Sande, 1995).

Host Factors

Host defenses can both impair and facilitate the formation of the vegetative lesion. Although humoral antibodies should decrease the numbers of circulating bacteria, they also may facilitate bacterial invasion by stimulating agglutination. Constant antigenic challenge results in the formation of circulating antibodies. Rheumatoid factors (anti-IgG IgM antibodies) develop in 50% of human patients within 6 weeks of developing IE. Antinuclear antibodies also are formed. Circulating immune complexes are more likely with long illnesses. Although antibodies may provide some protection, they also may contribute to the development of glomerulonephritis, musculoskeletal abnormalities, and low-grade fever. Interestingly, platelets provide the host with some defenses during the course of IE. Low-molecular-weight cationic proteins (thrombodefensins, or PMP) are released following exposure of the platelet to thrombin. These appear to damage the bacterial cell membrane or wall and may act synergistically with select antimicrobials to cause bactericidal effects. Organisms resistant to PMP may be more likely to contribute to the pathophysiology of IE (Sheld and Sande, 1995).

Complications of Infectious Endocarditis

Complications of IE that may require medical management develop in several organs. In humans, myocardial abscesses are found in 20% of cases autopsied, generally as a result of acute staphylococcal endocarditis. Embolism is common, most commonly occurring in the splenic, renal, heart (coronary), or cerebral circulation. The kidney is often an organ afflicted in patients with IE because of septic embolization (with or without abscessation), infarction, or glomerulonephritis. Cerebral emboli occur in 33% of human cases of IE, leading to arteritis, abscessation, and infarction. Splenic abscesses, although potentially common, may not be clinically evident. Petechiae may indicate arteritis of the vascular supply of the skin or immune complex deposition (Sheld and Sande, 1995).

Antimicrobial Therapy

Despite the low incidence of therapeutic success, venous blood culture is probably the most important diagnostic tool for IE. Multiple blood cultures (at least three are recommended in the first 24 hours for human patients) are more likely to yield a positive result. Bacterial counts in blood are generally low, and growth can be slow. Cultures should be held 3 weeks. Newer technologies may include methods that detect bacterial cell constituents.

Empirical therapy should begin after cultures have been collected. In human patients, *Staphylococcus* and *Streptococcus* species are among the most common causes of IE. In dogs, *S. aureus, E. coli,* and β-hemolytic streptococci are the most commonly isolated (O'Grady, 1995). Antimicrobial selection should be broadly based, however, targeting gram-negative as well as gram-positive organisms. Anaerobic organisms also should be included in the spectrum. The same approach is indicated for culture-negative IE. Drug distribution is less of a concern for IE, thus minimizing the need for lipid-soluble drugs. An exception must be made if bacterial embolization of organs (e.g., spleen, brain, or kidneys) has occurred or if the original source of infection remains a potential source of continuing infection. Antimicrobials should be based secondly on efficacy in the presence of potential immune suppression. Bactericidal concentrations should be achieved in blood or tissues, indicating intravenous therapy. Consideration should be given to release of endotoxin. Combination therapy should be considered not only to enhance the spectrum of a single antimicrobial but also to enhance efficacy. β-Lactams should be considered because of their broad spectrum as well as their ability to increase antimicrobial delivery into bacteria. Imipenem stands out among the β-lactams for its minimal release of endotoxin. Likewise, the fluorinated quinolones and the aminoglycosides cause minimal release of endotoxin.

Peritonitis and Other Intra-abdominal Infections

Pathophysiology

Infection of the abdomen includes infections of the peritoneal space, retroperitoneal space, and the viscera, including the liver, pancreas, spleen, and kidney (Levison and Bush, 1996). In veterinary medicine, peritonitis is most commonly secondary to an intra-abdominal infection. Bacteremia is a common finding in infections associated with aerobic organisms but less common if infection involves anaerobes. Bacteria can access the peritoneal cavity directly via transmural migration, through the (damaged) intestinal wall, or through other intra-abdominal abscess. In patients with liver disease, organisms that might otherwise be removed from portal circulation can access the peritoneum through lymph or blood. Fever, abdominal pain, nausea, vomiting, and diarrhea are common clinical signs associated with peritonitis. Analysis of peritoneal fluid collected by paracentesis should provide the basis of diagnosis and the need for surgical intervention. Surgical correction is indicated for both diagnostic and therapeutic intervention. Peritoneal fluid can also provide a basis for initial antimicrobial therapy as well as culture and susceptibility data.

The causative organisms of peritonitis are likely to vary with the source; each organ is characterized by its own natural flora. Gastric flora is variable, depending on the state of hydrochloric acid secretion, but can include flora from the oral cavity. The flora of the small intestine is also variable, but, in the presence of disease (including achlorhydria), the number of organisms also increases. Large bowel organisms can be present in small bowel obstructions, stasis, and so forth. *Escherichia coli*, enterococci, and anaerobes (e.g., *Bacteroides*, *Fusobacterium*, *Peptococcus*) are among the likely causative organisms. The primary flora of the large bowel are anaerobic.

Penetration of organisms into the peritoneal cavity generally is insufficient for the development of peritonitis. Chemical damage such as that associated with bile peritonitis may cause necrosis that increases the severity of peritonitis. The presence of free hemoglobin in the peritoneal cavity contributes to peritoneal infection, perhaps by providing iron required for bacterial metabolism. Intraperitoneal fluid and fibrin increase the inflammatory response to microbial organisms. Fibrin may serve to trap organisms, yet allow abscess formation. In addition, it causes abdominal organisms to adhere to one another. Bacteria produce a number of substances that contribute to the pathophysiology of peritonitis. Endotoxin concentrations increase rapidly in the presence of peritonitis; aerobic organisms possess more endotoxin with greater biologic activity than anaerobic organisms. Anaerobic organisms, however, produce collagenases and proteolytic and other enzymes. In addition, anaerobes may be more resistant to granulocyte killing mechanisms (Levison and Bush, 1996).

The mixture of organisms may contribute to the pathophysiology of infection and may increase (synergistically) the pathogenicity of infection. On the other hand, facultative organisms may facilitate the growth of anaerobic organisms by reducing the oxygen tension of the environment. Each bacterial component may contribute differently to the peritoneal infection. Early peritonitis may be characterized predominantly by infection with gram-negative aerobes; later peritonitis reflects abscessation by obligate anaerobes. Either stage can be lethal.

Antimicrobial and Adjuvant Therapy

Antibiotics should be used to control or prevent bacteremia, to limit infection locally, and to prevent an inflammatory response to infection. The presence of inflammation indicates a need for surgical intervention, including drainage of the abdomen. Therapy should begin immediately after cultures are collected, but antimicrobials should be modified based on data received after therapy has begun.

Infections are generally polymicrobial. Data generated from human patients are likely to be applicable to small animals (Levison and Bush, 1996). Antimicrobial therapy should target a mixed infection, with organisms most likely derived from the gastrointestinal tract. *Escherichia coli*, *Klebsiella*, *Enterobacter*, and *Proteus* are among the more common aerobic (but facultative anaerobic) organisms. In human patients, infection that develops during hospitalization most commonly involves highly resistant strains of aerobic gram-negative organisms: *Acinetobacter*, *Serratia*, and *P. aeruginosa* (Levison and Bush, 1996). *Bacteroides*, *Clostridium*, *Fusobacterium*, *Peptococcus*, and *Peptostreptococcus* are among the most common obligate anaerobic organisms. Antimicrobial therapy should include anaerobic organisms because they often are involved even when not present on culture. Several factors impair culture of anaerobic organisms. Cultures require longer time for growth and susceptibility testing. In addition, susceptibility data often have not been standardized for anaerobic organisms.

Data from human patients indicate that survival of peritonitis is decreased if initial therapy is inappropriate, even if "adequate" therapy is ultimately implemented (Levison and Bush, 1996). Thus, initial antimicrobial therapy is very important. Combinations of two or more antimicrobials are generally selected for treatment of peritonitis; however, care must be taken to avoid antagonistic combinations (see Chapter 8). Antimicrobials need not be effective against all organisms. Eradication of the most virulent organisms may remove the synergistic effect of multiple organisms, thus allowing host defenses to destroy organisms not removed by antibiotics. Clindamycin is particularly appealing because of its efficacy against approximately 95% of anaerobic organisms and has been effective as the sole agent in infections caused by mixed infections with anaerobic Enterobacteriaceae. In addition, it is effective against *Staphylococcus* species. Metronidazole is also a good choice because of its efficacy against anaerobes. In addition, it may have efficacy against *E. coli* in mixed aerobic-anaerobic infections. Among the β-lactams, the penicillins are preferred because of their efficacy against anaerobes compared with cephalosporins. β-Lactamase protectors provide enhanced efficacy against both aerobes and selected anaerobes. Imipenem has the broadest efficacy of the antimicrobials currently available; that of ticarcillin is also broad, especially when combined with clavulanic acid. Aminoglycosides are indicated for resistant aerobic gram-negative and selected positive organisms and provide synergistic activity when combined with β-lactams. They are not, however, efficacious against anaerobic organisms or in an anaerobic environment. Likewise, care must be taken in the selection of a first-generation cephalosporin. Cefoxitin, a second-generation drug, includes many gram-negative organisms and *Bacteroides fragilis* in its spectrum. The synergism expressed between fluorinated quinolones (e.g., enrofloxacin) and metronidazole in treatment of peridontitis may reasonably be expressed in treatment of peritonitis as well, suggesting that this combination is appealing.

Intravenous administration is recommended to maximize drug delivery to the gastrointestinal tract, which may be poorly perfused. Once gastrointestinal function is normal, oral administration can be reinstituted. Irrigation of the peritoneal area and the peritoneum is recommended. Although bactericidal activities of the host (specifically opsonins) may be diluted by irrigation, dilution of microbes and fibrin is of greater advantage. Addition of heparin will further reduce fibrin deposition and the risk of adhesions or pockets of microbial growth. Although povidone-iodine can decrease the incidence of intra-abdominal infection when used as an irrigant, it also may impair host defenses. More important, cytotoxicity and proinflammatory effects can worsen inflammation associated with peritonitis. Intraperitoneal administration of antibiotics does not appear to offer distinct advantages over intravenous administration. An exception is made with peritoneal dialysis as adjuvant therapy; antibiotics should be added to the peritoneal lavage to maintain antibiotic concentrations in the peritoneal fluid.

Prophylactic therapy includes use of preoperative cleansing with diet, as well as cathartics and enemas to reduce the total fecal and bacterial mass. Oral antibiotics should be used to cleanse the gastrointestinal tract. Gastrointestinal flora are sensitive to oral neomycin (aerobic gram-negative organisms) and metronidazole (anaerobes). Intravenous antibiotics should also be used preoperatively for patients for which the surgical procedure is accompanied by a high risk of contamination.

Peritoneal dialysis as a method of treating peritonitis should be accompanied by antimicrobial use. Contamination from organisms inhabiting the skin (e.g., *Staphylococcus* species) is the most common source of infection in patients receiving peritoneal dialysis as a means of controlling renal failure.

Sepsis and Septic Shock Syndrome

Definitions

Sepsis is defined by clinical evidence of a systemic response to an infection (such as tachycardia, fever, or hypothermia) (L.S. Young, 1995). Sepsis syndrome is sepsis characterized by altered perfusion of organs (e.g., respiratory or renal dysfunction), whereas septic shock is sepsis syndrome accompanied by hypotension that is responsive to pharmacologic intervention. Refractory shock, on the other hand, is septic shock that (in humans) lasts longer than an hour and does not respond to conventional pharmacologic therapy. The systemic inflammatory response syndrome can result from sepsis but may also indicate a response to any number of systemic mediators of inflammation. Multiorgan response and potential failure is involved. Note that none of these definitions is based on the presence of bacterial (or other microbial infection); rather, each is based on clinical signs. Presumably, at some time during the course of infection, bacteremia (positive blood cultures) and endotoxemia (presence of endotoxin in the blood) have been evident if a diagnosis is made. Regardless, because the syndrome can be a progressive, fatal clinical situation, management is intensive and meticulous.

Pathophysiology

Systemic disease caused by gram-negative bacteria is the most common cause of the sepsis syndrome. The lipid moiety of the lipopolysaccharide (LPS) covering of gram-negative organisms is the most common virulence factor. It is LPS that triggers the host response to bacterial invasion, including both humoral and cellular aspects. Cytokines and, in particular, tumor necrosis factor (TNF) and interleukin-1 (IL-1; the classic endogenous pyrogen) are produced by macrophages and monocytes within minutes of contact with LPS (Fig. 10–3). Each is capable of inducing fever and inflammation. Tumor necrosis factor in particular has been implicated as the most potent mediator of the pathophysiology of sepsis. Tumor necrosis factor alone, however, probably is not sufficient to be lethal; yet, when present with other released mediators and, in particular, interferon-γ, the effects of TNF become more lethal. The majority of lethal effects caused by TNF can be attributed to its effects on tissue metabolism, cardiac function, and vascular tone. Nitric oxide (endothelial relaxing factor) is being exposed as an important mediator of the lethal effects of TNF. The inducible nitric oxide synthase is the likely cause of hypotension associated with septic shock (L.S. Young, 1995).

Humoral mediators contribute to the systemic response to LPS. The coagulation pathway can be directly initiated by either LPS or TNF and other cytokines (most commonly through the extrinsic pathway). The fibrinolytic pathway also can be activated. Disseminated intravascular coagulopathy is not an uncommon sequelae of septic shock. Complement activation and platelet-activating factor contribute to the response. The inter-relationship between the mediators of septic shock is intricate and yet to be defined. These relationships, however, lead to the progressive nature of the syndrome, as well as the difficulty in pharmacologically manipulating response.

Antibacterial Therapy

Successful antimicrobial therapy of sepsis will be enhanced by anticipation (thus, looking for clinical signs), early diagnosis, aggressive yet appropriate antibiotic therapy, and intensive supportive therapy. Identifying the cause of sepsis (e.g., loss of gastrointestinal mucosal integrity, reversing granulocytopenia, removing foreign bodies) is an underlying focus of management. Although antibiotic therapy is the cornerstone of therapy, it can also contribute to the pathophysiology.

Combination antimicrobial therapy is a likely reason that patient response to antibiotics has improved (in human medicine) during the last several decades. For bacteremia, antimicrobial combinations should be chosen that provide a broad spectrum, enhance (synergistic) efficacy against gram-negative organisms, and minimize resistance. In the presence of sepsis, selected drugs should also minimize endotoxin release. Organisms particularly adept at developing resistance include *Pseudomonas, Serratia,* and *Enterobacter* species. Combination therapy is particularly important in neutropenic patients. Monotherapy, generally with imipenem, a fluorinated quinolone (e.g., enrofloxacin), or a third-generation cephalosporin (e.g., ceftazidime) may be effective if the cause is a highly susceptible gram-negative organism. Yet, the prudent clinician will use a combination of drugs likely to be effective against the suspected organism. Treatment regimens should be

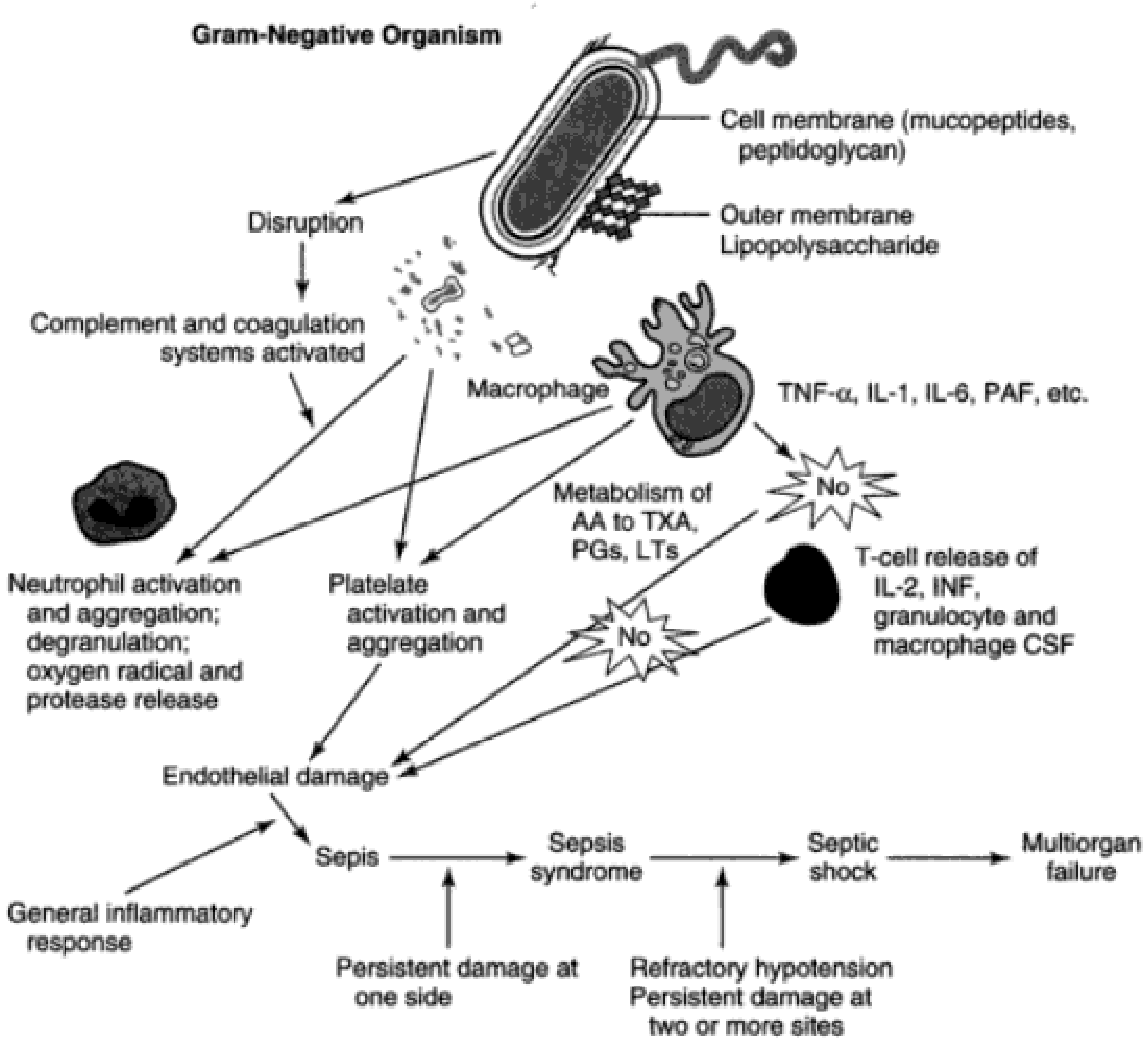
Gram-Negative Organism
Cell membrane (mucopeptides, peptidoglycan)
Outer membrane Lipopolysaccharide
Disruption
Complement and coagulation systems activated
Macrophage
TNF-α, IL-1, IL-6, PAF, etc.
No
Metabolism of AA to TXA, PGs, LTs
T-cell release of IL-2, INF, granulocyte and macrophage CSF
Neutrophil activation and aggregation; degranulation; oxygen radical and protease release
Platelate activation and aggregation
No
Endothelial damage
General inflammatory response
Sepis
Sepsis syndrome
Septic shock
Multiorgan failure
Persistent damage at one side
Refractory hypotension Persistent damage at two or more sites

Figure 10–3. The sequelae of endotoxemia. Selected antibiotics are more likely to cause endotoxin release, most notably the β-lactams (with imipenem being an exception). The aminoglycosides cause little endotoxin release. AA = amino acids; CFS = cerebrospinal fluid; IL = interleukin; INF = interferon; LTs = leukotrienes; PAFs = platelet-activating factor; PGs = peptidoglycans; TNF-α = tumor necrosis factor-α; TXA = thromboxane A.

changed if indicated by culture and susceptibility data. Design of dosing regimens is discussed in Chapter 8; monitoring as a tool to ensure adequate drug concentrations is particularly important for the septic patient.

Adjuvant Therapy

A number of adjuvant therapies are critically important to the patient suffering from septic shock. Cardiovascular support can be provided in the form of volume replacement and positive inotropes/pressors. Fluid therapy should be intensive with the goal of reestablishing normal perfusion. A number of colloids and some crystalloids are available. Drugs intended to maintain or increase blood pressure should be used cautiously. Certainly, adrenergic agents such as dopamine, dobutamine, norepinephrine, or isoproterenol should be administered only in the presence of adequate volume replacement and in conjunction with intensive monitoring of central venous pressure and, ideally, pulmonary wedge pressure. Fluid therapy is likely to need to be more intensive in the presence of pressor agents, dobutamine in particular. Although dopamine at low doses (5 μg/kg per minute) may be preferred in the presence of impaired renal perfusion, dobutamine is probably preferred otherwise. Of the two, dobutamine (5 to 10 μg/kg) is more likely to increase oxygen delivery and consumption in tissues (Hardie, 1996). The advent of oliguria or anuria indicates the need for diuretic therapy. Opiate antagonists have been shown to reverse the course of septic shock in selected studies. Because patients with prolonged hypotension were particularly responsive, it is likely that the drugs (e.g., naloxone) provide a transient vasopressor effect. Naloxone, however, appears to have no clinically relevant effect in patients in septic shock.

Thromboembolism can be a life-threatening complication of septic shock. Correction or prevention of impaired tissue perfusion (i.e., with fluid replacement or pressor agents) helps prevent decreased microcirculation. Additional preventative measures might be implemented in the presence of normal platelet counts and coagulation times. Synthetic colloids (which themselves can prolong bleeding times), or the combination of crystalloids and low-dose heparin, are indicated to maintain microcirculatory flow. Evidence of disseminated intravascular coagulation (prolonged coagulation times and low antithrombin III and platelet counts) indicates the need for replacement of coagulation factors. Heparin therapy should be implemented with caution in the presence of disseminated intravascular coagulation to minimize the risk of bleeding. Certainly, heparin therapy is indicated in the presence of pulmonary thromboembolism.

The role of drugs intended to ameliorate the signs of sepsis syndrome is controversial. Glucocorticoids, nonsteroidal anti-inflammatories, and lazeroids (an investigational category of drugs—see corresponding chapters) are variably effective to noneffective, depending on the study. The most important variabilities that appear to affect response to these drugs is dose and timing of administration. For glucocorticoids, most studies in human patients afflicted with sepsis have failed to show a significant benefit to survival; some patients dosed with glucocorticoids were more likely to develop suprainfections. Yet, experimental studies have shown that, when provided sufficiently early (within 4 hours of sepsis), "shock" doses of glucocorticoids may ameliorate release of the more important mediators of septic shock. Similarly, nonsteroidals (and, in particular, flunixin meglumine) may decrease the release of or response to a number of mediators of septic shock (Hardie et al., 1983). Again, however, timing of administration is critical: Benefits are most likely to be realized when administration occurs within several hours of the onset of sepsis. Unfortunately for veterinary patients, clinical signs of sepsis are usually not identified until the critical period of anti-inflammatory administration has passed.

The advent of recombinant technologies has led to the development of granulocyte colony-stimulating factors. These drugs are likely to prove useful for selected patients (most notably granulocytopenic patients). Treatment protocols have not, however, been well established. Therapy with antiserum has enjoyed a resurgence of interest in human medicine. Administration of serum from patients that have recovered from shock induced by *Pseudomonas* species or patients "immunized" with mutant strains of *E. coli* has increased the survival of patients suffering from profound shock. Monoclonal antibodies that bind endotoxin, TNF, and other mediators of shock have been or are being studied. Pentoxifylline is a methylxanthine derivative that is accompanied by properties not present in other methylxanthines. Among those potentially beneficial in sepsis is the ability to scavenge oxygen radicals and alter the rheologic properties of blood, thus facilitating microcirculation. The use of low doses of an antibiotic that binds endotoxin (e.g., polymyxin B) yet is otherwise nephrotoxic apparently has not been studied in small animals.

Prophylaxis remains an important tool for the prevention of sepsis. Among the more important in the critical care environment is meticulous adherence to cleanliness policies in the environment to minimize nosocomial infections. Prophylactic antimicrobials are discussed later.

MISCELLANEOUS INFECTIONS

L-Form Bacterial Infection

L-form bacteria lack or have a deficient cell wall. Their role in causing infections in animals is not well identified. A number of organisms are capable of becoming cell wall deficient, including *Staphylococcus* and *Streptococcus* species. Information regarding the causes of an organism assuming this structural state are not clear, nor is the role of L-forms in the cause of disease. Presumably, the infection starts in the skin and progresses as multiple abscesses form and then dehisce. Bacteremia can lead to polyarthritis. Because of their cell wall-deficient state, microorganisms are difficult to detect by light microscopy but can be visualized inside phagocytes by electron microscopy. Drugs whose antibacterial effects do not target the cell wall are indicated. Tetracyclines have been the drug of choice (Greene, 1995).

Brucellosis

Pathogenesis

Brucellosis as an infectious disease draws attention because of its insidious nature, difficulty in treatment, and zoonotic potential. *Brucella canis*, the causative agent of brucellosis in dogs, is a small gram-negative coccobacillus. Among *Brucella*, *B. canis* stands out in morphology, biochemistry, and immunology. Among its differences compared with other organisms is its zoonotic potential: The disease can be transmitted only between members of Canidae. Cats are only transiently infected after experimental infection. Dogs are susceptible to infection with *B. abortus* but do not appear to be important to the spread of infection. Infection by *Brucella* involves penetration of mucous membranes after contact with contaminated fluids from an infected urogenital tract or an aborted fetus. Phagocytized organisms are transported to lymphatic and genital tissues, where multiplication occurs. Leukocyte-associated bacteremia can persist for years. Organisms can be intermittently shed from infected animals (during estrus, breeding, or abortion) (Carmichael and Greene, 1998).

Although antibodies are generated against *Brucella* species, as with most intracellular organisms, cell-mediated immunity is the primary mechanism of host defense. Cell-mediated immunity can provide protection against reinfection, although persistent infection may be necessary to provide persistent protection. Immune response to inflamed infected tissues (e.g., spermatozoa) contributes to infertility. Immunosuppressive drugs appear to increase risk of infection but may not alter the course of the disease in dogs already infected. Spontaneous recovery can occur but may take up to 5 years. During this time period, infection might be associated with bacteremia. As with other blood-borne organisms, *Brucella* may localize in tissues other than the urogenital tract. Discospondylitis, anterior uveitis, and, less commonly, glomerulopathy or meningoencephalitis may result. Diagnosis is based on agglutination tests, agar-gel immunodiffusion, or enzyme-linked immunosorbent assay (Carmichael and Greene, 1998). Therapy with antibiotics does alter the progression of the disease.

Antimicrobial and Adjuvant Therapy

A number of antimicrobial drugs are effective in vitro against *Brucella* but may not be able to eradicate infection. Antimicrobial therapy can relieve symptoms, shorten the duration of illness, and reduce the likelihood of complications yet not eradicate the organism (E.J. Young, 1995). Success will be enhanced by a combination of effective drugs at high doses for at least 4 weeks. Drugs should be able to penetrate cell membranes; accumulation in phagocytic cells should further facilitate success. Among effective antimicrobials, lipid-soluble tetracyclines (minocycline and doxycycline) are particularly efficacious when used at a high dose and in combination with an aminoglycoside. The World Health Organization has also recommended doxycycline in combination with rifampin, although doxycycline with streptomycin was found to be more effective in the treatment of discospondylitis (E.J. Young, 1995). Fluorinated quinolones should also be effective when combined with aminoglycosides (E.J. Young, 1995), although clinical trials documenting efficacy in dogs have not been reported. An added advantage of these drugs is intracellular accumulation. Fluorinated quinolones may not, however, be effective as sole agents against brucellosis. Human patients intolerant of tetracyclines also responded well to combinations of trimethoprim/sulfonamides and aminoglycosides. Antimicrobial therapy should not be discontinued too early; sequential titers can be used to assess response to therapy.

Infected dogs should be neutered as soon as possible. Glucocorticoids or other immunosuppressive therapy may be indicated for treatment of infections associated with life-threatening or organ-threatening inflammation (i.e., CNS). Currently, prevention is best implemented through good hygiene practices, neutering of infected animals, and vaccination of cattle.

Leptospirosis

The genus *Leptospira* belongs to the family Treponemataceae, which contains all spirochetes, including *Borrelia* species. Leptospirosis is primarily a disease of wild and domestic animals, with humans becoming infected only occasionally (Farrar, 1995).

Pathogenesis

Leptospirosis generally causes an acute generalized infection or interstitial nephritis. Leptospires are motile spirochetes; *Leptospira interrogans* tends to be the pathogenic organism in animals. At least three antigenically distinct serovars cause disease in dogs; infection in cats is rare (Greene, 1990; Greene, 1998a). Infection occurs through the mucosa or abraded skin and can occur between animals or in animals that come in contact with the contaminated environment. Once the mucosa is penetrated, the organism multiplies rapidly in the bloodstream. Inflammation causes parenchymal damage, particularly in the liver and kidney. Persistence in renal tubular cells leads to colonization of the kidney (Farrar, 1995). Chronic active hepatitis can be a sequela of infection in dogs.

Leptospirosis can present as a peracute infection manifested by shock and death. Less acute presentation presents as fever, anorexia, vomiting, and dehydration. Clinical laboratory tests may reveal thrombocytopenia, electrolyte alterations, and liver damage. Diagnosis is based on serologic testing (paired serum titers). Leptospires are very difficult to recover, with urine analysis by darkfield microscopy providing the best chance of discovery.

Antimicrobial Therapy

Treatment focuses on eradication of the causative organism and supportive therapy. Acute renal failure may require intensive management with diuretics. Antibiotics should inhibit the multiplication of the organism as well as eradicate it. Response manifested as a decrease in fever should be apparent within several hours of administration (Greene, 1998a). Drugs shown effective in vitro include most penicillins, third-generation cephalosporins or tetracyclines, but not first-generation and second-generation cephalosporins. Not all penicillins appear to be able to eradicate the organisms, but penicillin G, ampicillin, and amoxicillin are among the effective drugs (Farrar, 1995). In animals, penicillin clears infection with leptospirosis; aminoglycoside therapy (or tetracyclines) can be used to resolve the carrier state after recovery (Greene, 1995), although doxycycline can also be used for initial therapy (Greene, 1998a). In human patients, doxycycline appears to be beneficial for the prevention of infection even postexposure, whereas the penicillins do not appear to prevent infection postexposure (despite their ability to eradicate infection; Farrar, 1995). Fluorinated quinolones (ciprofloxacin and enrofloxacin) also appear to be effective against leptospires, although clinical studies supporting their use are lacking. Hamsters experimentally infected with *L. interrogans* responded to ciprofloxacin (Shalit, 1989). In vitro studies of five serovars of *Leptospira* indicated efficacy based on MICs (0.05 to 0.20 μg/mL), although the effect was bacteriostatic; bactericidal concentrations were 10- to 100-fold higher (Takashima, 1993). Orbifloxacin has proved ineffective (Greene, 1998a). Experimentally, the macrolides also appear effective (Greene, 1998a). Protection is best implemented by prevention of exposure and elimination of reservoirs.

Lyme Borreliosis

Like *Leptospira* species, *Borrelia* species belong to the family Treponemataceae. *Borrelia* are motile spirochetes that have an outer slime-like layer. They are rapidly killed by desiccation and ultraviolet lights. *Borrelia* infect both humans and animals; up to 15 *Borrelia* species cause disease. The Centers for Disease Control and Prevention has designated Lyme disease as the most common vector-borne infection in the United States. The disease may, however, also be overdiagnosed in humans (Steere, 1995).

Ixodes species are the primary insect vectors of the spirochete *Borrelia burgdoferi*. Lyme borreliosis afflicts primarily humans and dogs, although cats can be infected experimentally. Organisms are able to adhere to many different types of mammalian cells as well as avoid elimination by phagocytic cells (Steere, 1995). The immune response appears to be initially suppressed during infection, apparently allowing the organisms to spread. The disease is multisystemic, with nonspecific clinical signs including relapsing fever (during which borreliae are present in blood), anorexia, lethargy, and lymphadenopathy. Polyarthritis might result in episodic lameness; clinical signs often do not develop until several months after infection (Steere, 1995; Greene, 1998b). Heart block, which occurs in humans (Steere, 1995) has been reported in one infected dog. Clinical laboratory changes are also variable, depending on the site of localization of the infection. Diagnosis is facilitated by serum titers, although interpretation is complicated by interlaboratory variability and overlap between titers indicative of clinical versus subclinical infection. Resolution of natural disease in humans appears to be dependent on class II major histocompatibility complex genes.

Based on in vitro testing, antimicrobials effective against *B. burgdorferi* include, in order from most to least effective, ceftriaxone, erythromycin, amoxicillin, cefuroxime, doxycycline, tetracycline, and penicillin G (Greene, 1998b). Antimicrobial therapy based on clinical response includes, in order of preference, tetracyclines (doxycycline is the drug of choice), high doses of ampicillin or amoxicillin, and erythromycin and its derivatives

(Steere, 1995). Third-generation cephalosporins (e.g., ceftriaxone) are also generally effective. The organisms appear to be resistant to ciprofloxacin (and presumably enrofloxacin and other veterinary fluorinated quinolones) and to the aminoglycosides. Oral therapy is sufficient except in cases of neurologic signs; IV therapy should be instituted in such cases. *Borrelia burgdorferi* is a potent inducer (in vitro) of TNF-α and interleukin-1β. Antimicrobial therapy in humans is occasionally characterized by a Jarisch-Herxheimer reaction, which may reflect release of spirochetal endotoxin and subsequent septic shock syndrome (Steere, 1995). Supportive therapy includes nonsteroidal anti-inflammatories as needed for joint lameness. Disease-modifying chondroprotective agents should be strongly considered. Care should be taken with combining nonsteroidals with doxycycline or minocycline due to competition for protein-binding sites and the potential for adverse reactions to the nonsteroidal drug. Glucocorticoids should be limited to treatment of acute spirochetemia; recrudescence of spirochetemia will be facilitated with their use. Prevention focuses on eradication of the vector.

Higher Bacteria: Nocardiosis and Actinomycosis

Pathogenesis

Nocardiosis is generally presented as a localized infection. The organism is an acid-fast, aerobic, soil-borne actinomycete, usually introduced through the respiratory tract. Traumatic penetration may result in a localized skin infection (Lerner, 1995; Russo, 1995). *Actinomyces* are commensal anaerobic organisms found in the oral cavities of animals. Infection commonly follows penetrating wounds, such as inhalation of grass awns. *Actinomyces* are distinctive in their configuration, presenting as filamentous growth with true branching.

The taxonomy of *Nocardia* is currently evolving, but *Nocardia asteroides* is among the more commonly identified pathogens. Culture is made difficult sometimes by the slow growth which characterizes this organism when present in mixed cultures from clinical material. Rapidly growing bacteria often obscure the smaller *Nocardia* colonies. Colony characteristics may take up to 2 to 4 weeks to be noticed. Gram staining may help identify the organisms earlier, although smears may also be negative. *Nocardia*, but not *Actinomyces*, stains acid fast, although acid-fast staining in *Nocardia* is also variable. *Nocardia* appears as beaded, branching filaments when Gram stained but will not stain with hematoxylin and eosin preparations or in periodic acid-Schiff stains for fungi (see Chapter 8, Fig. 8–11) (Lerner, 1995). In human patients, positive cultures and smears occur only in one third of the cases. Pus from a fistula or abscess will facilitate identification. *Nocardia* and *Actinomyces* also stain Gram positive, but again staining is irregular (Hardie, 1990).

Nocardiosis is an opportunistic infection. In humans, a number of underlying diseases, most of which are accompanied by an altered immune system, predispose the patient to nocardiosis. Infections occur because the organism is able to evade bacterial protective mechanisms of the host. Immune T cells and neutrophils are important to eradication of *Nocardia*. *Nocardia* may be resistant to oxidative bursts of neutrophils. Filamentous log-phase cells of *Nocardia* are more virulent and toxic to macrophages than are the coccoid stationary-phase organisms, which can be easily phagocytized.

Nocardia produces suppurative necrosis and abscess formation. In humans, *Nocardia* in skin seldom causes a marked fibrotic response; rather, granulation tissue will be loose, with bands of fibrous tissue surrounding the lesions. Confluent abscesses form with little to no encapsulation. Extension to the pleura or chest wall may result in empyema, subcutaneous abscesses, or sinus tracts. Occasionally, bony involvement may occur. Calcium-containing "sulfur granules" present a barrier to bacterial penetration and may indicate reversion of the organism (*Actinomyces*) to an L-form.

Antimicrobial and Adjuvant Therapy

A number of antimicrobials are effective against both *Actinomyces* and *Nocardia*. An anaerobic environment and, hence, infection with *Actinomyces* should be assumed unless proved otherwise, thus leading to more conservative antimicrobial selection. Penicillins (penicillin G, amoxicillin) remain a drug of choice, although resistance and L-form organisms can preclude their efficacy (Hardie, 1990). Clavulanic acid can reduce the risk of resistance. The formation of protective calcium granules by certain strains of *Actinomyces* limits antibiotic penetration into the organisms. The formation of these granules is stimulated by the presence of penicillin antibiotics. Trimethoprim/sulfonamide combinations are also very effective, although high doses are recommended. Combinations of penicillins with trimethoprim/sulfonamide result in synergistic actions against *Nocardia* and *Actinomyces* (Eliopoulus and Moellering, 1996) and are the authors' most common first choice (at high doses and frequent intervals). Clindamycin and erythromycin are also effective, particularly against L-forms (Hardie, 1990). The aminoglycosides are highly effective against *Nocardia* and *Actinomyces*, and synergistic activity has been documented against this organism with combinations. Minocycline (and presumably doxycycline) also is effective, although use of this bacteriostatic drug may preclude combinations with other antimicrobials.

Treatment for both *Nocardia* and *Actinomyces* should occur for at least 6 weeks, with high doses at frequent intervals (see Respiratory Tract Infections in this chapter). Treatment should continue beyond resolution of clinical signs. Adjuvant therapy should include drainage and lavage of empyema and, when indicated, chest tube drainage or surgical débridement. Lavage should continue for several days until cytologic examination of aspirated fluid indicates resolution of infection and fluid accumulation decreases (5 to 10 days) (see previous discussion of empyema). The author has often recommended initial hospitalization and IV therapy with amikacin and amoxicillin/clavulanic acid or, for increasingly resistant organisms, imipenem followed 10 to 14 days later with very high (45 to 60 mg/kg twice daily) oral sulfadiazine, trimethoprim replacing the aminoglycoside. The amoxicillin/clavulanic acid combination should be continued with the sulfonamide for 4 to 6 weeks or more. The β-lactam should be administered at 6- to 8-hour intervals.

Mycobacteria

Mycobacteria are composed of a number of aerobic, acid-fast bacteria. They vary markedly in host affinity and ability to cause disease. Disease is frequently accompanied by granulomatous inflammation because of their ability to survive phagocytosis. The acid-fast nature of these microorganisms reflects the large amount of lipid material in the cell wall. Constituents of the cell wall stimulate the granulomatous response. The organisms are more resistant than most organisms to environmental changes (e.g., pH, heat) and are more resistant to disinfection. Some organisms (most notably *Mycobacterium avium*) can survive in the environment for several years. They are, however, very susceptible to 5% phenol or 5% household bleach. Generally, organisms causing disease are characterized by one of three forms (Greene, 1995). *Tuberculosis* generally is internal in location. Infecting organisms include *M. tuberculosis* (more common in dogs) and *M. bovis* (more common in cats). *Leprosy* is characterized by localized cutaneous nodules; *M. lepraemurium* is probably the most common infecting organism (in cats). *Atypical mycobacteria* is generally presented as a spreading subcutaneous inflammatory disease; among the several organisms causing this complex is *M. avium*. Dogs and cats are most commonly infected by owners with disease or exposure to infected farm animals.

Tuberculosis

Dogs and cats are more susceptible to infection by tuberculous mycobacteria than by atypical mycobacteria. Infection generally occurs through the respiratory or alimentary tract. Local multiplication at the site of infection results in a granulomatous response at the primary "complex" (site of deposition) and local lymph nodes. Particularly in cats, however, a granulomatous response may develop only in surrounding lymph nodes. For tuberculosis, respiratory infections are more common in dogs; intestinal infections are more common in cats. Infection can be followed by elimination of the organisms in animals with a sufficient immune response. The more common sequelae are location within phagocytic cells, intracellular multiplication, and granuloma formation as the body attempts to eradicate the organism. Organisms that outpace the host immune system can cause disseminated disease. Immunity is incurred by the cell-mediated response, but factors that facilitate an adequate response in the host are not known. Diagnosis can be facilitated with intradermal skin testing in dogs with the highest concentration of antigen used in humans. Cats do not react strongly to intradermal testing. Diagnosis can be facilitated by the presence of acid-fast organisms in tissue biopsy material.

Antimicrobial therapy is complicated by the fastidious nature of the organism. Drug penetration into the organism is likely to be more difficult than for other organisms; intracellular survival further complicates efficacy of drugs reaching the site of infection. Treatment should generally include combination therapy for at least 6 to 9 months. A combination of isoniazid (10 to 20 mg/kg orally once daily) plus rifampin (10 to 20 mg/kg orally every 12 to 24 hours) plus ethambutol (15 mg/kg orally every 24 hours) is the most effective therapy (in humans), although isoniazid-resistant organisms have become increasingly more difficult to treat. More rapid remission is likely with IV administration. The isoniazid can also be administered prophylactically (6 to 12 months) in cases of exposure. The fluorinated quinolones are also effective against selected species of mycobacteria. *Mycobacterium avium* (see later discussion of atypical mycobacteria) is an exception, although it does also respond to other drugs used to treat atypical mycobacteria. Infected animals remain a health hazard because they serve as temporary sources of dissemination in the environment.

Leprosy

Feline leprosy is caused by *M. lepraemurium*, also the causative organism of rat leprosy. The infection causes rapidly growing, soft, fleshy nodules in the skin and subcutaneous tissues, usually on the head or extremities. Infected cats are generally healthy, and the lesions are not painful. Diagnosis is generally based on the presence of granulomatous inflammation and acid-fast organisms in biopsy specimens or impression smears. Treatment includes surgical removal and antimicrobial therapy. Drugs include dapsone (1 mg/kg [dogs] orally every 8 hours or 50 mg [cats] orally every 12 hours) for 2 weeks or clofazimine (8 mg/kg orally every 24 hours for 6 weeks and then twice weekly thereafter). Rifampin may also be useful. The safety of these drugs has not been established for cats.

Atypical Mycobacteria

Both slow-growing organisms (*M. avium*) and rapid-growing organisms (e.g., *M. fortuitum, M. chelonei*) cause disease in dogs and cats, although the rapid organisms are more common. These organisms are ubiquitous in nature (especially wet soils) and generally are not pathogenic. Infection is generally acquired from trauma to the skin; the location of entrance into the body determines the presentation of the disease. Penetration into subcutaneous tissue appears to promote pathogenicity. Generally, infection presents as a localized, but spreading, infection characterized by granulomatous inflammation and acid-fast organisms. Multiple fistulous draining tracts are evident, usually in the caudal abdominal, inguinal, or lumbar subcutaneous tissues (Fig. 10–4). Cats are usually clinically healthy even if cutaneous involvement is extensive. Less commonly, fever, anorexia, and weight loss occur. Hypercalcemia as a result of the release of parathormone-like hormone from macrophages associated with the inflammatory response has been documented in our hospital. Diagnosis is difficult in part because organisms are not abundant. Tissue biopsy specimens should be taken from the subcutaneous tissues because organisms are more likely to be located in the panniculus. Nocardiosis should be considered as a differential. Bacterial culture provides the definitive diagnosis.

Therapy focuses on antimicrobial drugs. Antitubercular

Figure 10–4. Atypical mycobacterium in a cat before *(A)* and 3 months after *(B)* treatment with a combination of enrofloxacin and sulfadiazine/tribrissen. Note the granulomatous tissue and multiple fistulous tracts. (Photographs courtesy of Katrina Mealey, Washington State University, Pullman, WA.)

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drugs are generally ineffective against atypical mycobacterial species. Quinolones, aminoglycosides (particularly amikacin), and doxycycline (or minocycline) are effective and can be combined with one another if more aggressive therapy is desired. Other drugs that might be beneficial include trimethoprim/sulfonamide combinations and clofazimine. High doses are recommended to maximize drug delivery into the granulomatous tissue. Surgical debulking may be indicated for large granulomatous masses. Care should be taken to not discontinue drugs too early. Four to 6 weeks or more of therapy should be anticipated.

Melioidosis and Tularemia

Melioidosis is caused by *Burkholderia (Pseudomonas) pseudomallei*, a bipolar, aerobic, gram-negative motile bacillus occurring predominantly in Southeast Asia, Northern Australia, and the South Pacific. It is characterized by fever, myalgia, dermal abscesses, and epididymitis (Greene, 1998c). Effective antimicrobials include tetracyclines, chloramphenicol, trimethoprim-sulfonamide combinations, amoxicillin-clavulanic acid, and novobiocin-tetracycline. Two weeks of high doses of parenteral ceftazidime has proved most effective; imipenem-cilastin may also be effective.

Tularemia, caused by *Francisella tularensis*, is a tick-transmitted disease of both dogs and cats (Kaufman, 1998). Infection begins with localized lymphadenopathy followed by bacteremia and multiple organ involvement. Clinical signs vary and include fever, mucopurulent nasal or ocular discharge, abscess at the site of inoculation (or associated with lymphadenopathy), myalgia, shivering, and signs indicative of septicemia. Preferred antimicrobial therapy in human patients includes the aminoglycosides. Chloramphenicol or tetracyclines may be associated with relapses. The fluorinated quinolones also may be effective.

RICKETTSIAL DISEASES

Rickettsia are fastidious, obligate intracellular parasites that appear as pleomorphic coccobacilli. They multiply by binary fission, contain both DNA and RNA, and are capable of synthetic and energy-producing reactions. Their life cycle involves insect reservoirs (primarily ticks) and mammals (Saah, 1995). The rickettsial organisms include three families: Rickettsiaceae, Bartonellaceae, and Anaplasmataceae. The family Rickettsiaceae is further divided into three tribes: Rickettsiae, Ehrlichieae, and Wolbachieae. Within the Rickettsiae tribe are three genera: *Rickettsia, Rochalimaea,* and *Coxiella* (Breitschwerdt, 1995). Those organisms in the *Rickettsia* genera are broadly categorized further into two groups: that containing the causative agent of Rocky Mountain spotted fever and the typhus group. *Coxiella burnetii*, the causative agent of Q fever, is not included in either group and stands out additionally because of its robust nature outside of host cells and presentation of disease (Saah, 1995). The tribe Ehrlichieae also contains three genera: *Ehrlichia, Cowdria,* and *Neorickettsia* (Breitschwerdt, 1995).

Although advances in recent years have increased our knowledge regarding the physiology of these organisms and the pathophysiology of the disease, much information is still missing. The pathogenesis of the other rickettsial organisms reflects vasculitis due to proliferation of the organisms in endothelial cells. Diagnosis is generally based on serologic testing. Serologic evidence of disease generally does not, however, occur until several weeks after clinical signs have developed.

Ehrlichiosis

Causative Organisms

Disease caused by canine ehrlichiosis generally targets blood-forming units. Ehrlichiosis is caused by *Ehrlichia canis,* the brown dog tick, and *Rhipicephalus sanguineus* serves as the primary insect vector. Other infections carried by this vector (*Babesia canis* and *Hepatazoon canis*) can simultaneously infect the host. *Ehrlichia canis* is a pleomorphic organism that circulates in peripheral monocytes. Infection is transmitted through the saliva of the tick into the bloodstream of the host. Transmission has also occurred between hosts (patients) through blood transfusions.

Pathophysiology

Disease can present in an acute, clinical, or subclinical phase. The acute phase lasts 2 to 4 weeks, during which the organisms replicate in the mononuclear phagocytic cells of the liver, spleen, and lymph nodes. Infected cells travel to the lung, kidney, and meninges, where endothelial inflammation can occur. Nonspecific clinical signs during this phase include fever, anorexia, weight loss, ocular and nasal discharge, and edema. Additional clinical signs depend on the severity of infection in each organ and include dyspnea, neurologic abnormalities, and lymphadenopathy. Platelet consumption, sequestration, and destruction contribute to thrombocytopenia, which often characterizes this phase. Leukopenia and anemia become more likely as the disease progresses. The subclinical phase occurs at 6 to 9 weeks and is characterized by pancytopenia. An adequate immune response should eradicate the disease, but immunoincompetence leads to chronic infection. Clinical signs in chronic disease vary with the severity of infection and can range from asymptomatic to severe. Bleeding tendencies, anemia, chronic weight loss, and debilitation are nonspecific clinical signs. Abdominal tenderness, ophthalmic complications (anterior uveitis, retinal detachment), and neurologic abnormalities may be present. Secondary infections (bacterial and, less commonly, fungal) may reflect immune suppression. Diagnosis is based on clinical laboratory changes and serologic diagnosis using indirect fluorescent antibody. Treatment is oriented toward eradication of the infecting organism and supportive therapy based on clinical signs. Therapy in chronic stages may also need to target opportunistic infections in the immunosuppressed animal.

Antimicrobial and Supportive Therapy

Tetracyclines are the treatment of choice for ehrlichiosis. Lipophilic tetracyclines such as minocycline and doxycycline may be preferred because of better tissue penetrability, particularly for chronic cases. Although fluorinated quinolones (e.g., enrofloxacin) appear to be effective for the treatment of *Rickettsia rickettsii* at a dose of 3 mg/kg orally twice daily, based on experimental infection, they do not appear to be effective at 10 mg/kg orally twice daily for the treatment of ehrlichiosis (Neer, 1999). The effects of combination therapy with doxycycline and enrofloxacin on antimicrobial efficacy against ehrlichiosis have not been established, but the combination might be considered for patients that do not respond to doxycycline. Chloramphenicol is also effective against ehrlichiosis but is less ideal clinically than tetracyclines and enrofloxacin. Imidocarb diproprionate is also effective against ehrlichiosis, but care must be taken to minimize the side effects of this drug. It recently has been approved in the United States. It should be used to treat patients that have not responded to doxycycline or enrofloxacin.

Supportive therapy for ehrlichiosis includes fluid and electrolyte therapy, blood or blood component transfusions, hematinics (vitamins, iron if bleeding has been extensive), and, less commonly, drugs that stimulate erythropoiesis. Anabolic steroids should be used cautiously in the presence of liver involvement.

Serologic titers generated by ehrlichiosis are not protective, and reinfection may occur. Long-term prophylaxis might be considered in endemic areas or kennels and consist of tetracycline (6 mg/kg once daily orally) or reposital tetracycline (200 mg intramuscularly twice weekly).

Rocky Mountain Spotted Fever

Causative Organism

The causative agent of Rocky Mountain spotted fever is *Rickettsia rickettsii.* It is transmitted primarily by *Dermacentor* species, with the American dog tick being the principal vector in the eastern United States and the wood tick the principal vector in the western United States. Transmission of disease requires tick attachment to the host for at least 5 hours and up to 20 hours; thus, the disease might be prevented by routine "tick checks" (Breitschwerdt, 1995). The incidence of infection in dogs caused by this organism only now is being appreciated. Unrecognized and untreated illness can lead to death, although the severity of clinical signs depends, in part, on the degree and location of the initial vascular damage induced by the organisms. Diagnosis is complicated by cross-reactivity to several nonpathogenic members of *Rickettsia* and should be based on both acute and convalescent serum titers or direct immunofluorescence in skin biopsy material (Breitschwerdt, 1995).

Pathophysiology

Organisms are transmitted through the saliva of the tick into the bloodstream, where they replicate in endothelial cells of small blood vessels and capillaries. Damaged endothelial cells become inflamed. Vessels become permeable, causing extravasation of fluid into perivascular spaces. Depending on the severity of infection, clinical signs may indicate edema, hemorrhage, hypotension, or shock. Infection in vessels of the CNS may lead to neurologic signs and a more rapid deterioration of clinical signs.

Other clinical signs vary and may require medical management, depending on which organs are infected: Cardiac abnormalities may include conduction abnormalities or other life-threatening arrhythmias; the respiratory system may be characterized by clinical signs reflecting pulmonary edema, which is minimally responsive to diuretic therapy; ocular abnormalities range from subconjunctival inflammation to retinal detachment; and, in severe cases, acute renal failure occurs due to decreased renal perfusion. Severe inflammation causing vascular obstruction can lead to gangrene of peripheral limbs, ears, lips, scrotum, or mammary glands. Other less specific clinical abnormalities include fever, anorexia, depression, muscle pain, polyarthritis, and weight loss (Breitschwerdt, 1995). In addition to increases in liver enzymes and serum bilirubin, clinical laboratory tests may reveal the need to treat thrombocytopenia; severe acute infection may also cause leukopenia and anemia. Hypoproteinemia, azotemia, hyponatremia, and hypocalcemia may also be present. Treatment is focused on both eradication of the organisms and supportive therapy of derangements in the infected body system.

Antimicrobial and Supportive Therapy

Tetracyclines remain the treatment of choice of rickettsial infections. Although tetracycline may be sufficient, drugs characterized by better lipophilicity (e.g., doxycycline or minocycline) may be more advantageous. Chloramphenicol is also effective, but less so than tetracyclines. Fluorinated quinolones are also effective experimentally (Breitschwerdt, 1995), although clinical efficacy has not been established. Combinations of both doxycycline and enrofloxacin may be additive to synergistic, but the effects of this antimicrobial combination on rickettsial organisms has not been established. Clinical response should be rapid except in cases with severe vascular sequelae (i.e., neurologic or renal damage). Supportive therapy should target abnormalities previously described. These include electrolyte abnormalities and replacement of colloid (protein). Vascular permeability, however, will complicate volume replacement (with either crystalloids or colloids) and, if too intensive, may contribute to peripheral (including pulmonary) edema.

Other Rickettsial Diseases

Canine cyclic thrombocytopenia is caused by *Ehrlichia platys*, an organism that replicates in platelets. Cyclic thrombocytopenia occurs at 10- to 14-day intervals. Both platelet numbers (as low as 20,000) and aggregation are impaired. Treatment should be with tetracyclines as described for *E. canis. Neorickettsia helmintheca* is one of the causative agents of salmon poisoning disease, which is transmitted after ingestion of fish containing the trematode vector. Like other rickettsial diseases, it is treated with tetracyclines. Hemobartonellosis is caused by a hemotrophic organism that causes acute or chronic anemia in dogs or cats. Damaged red blood cells are removed by the host's immune system. The host is not able to resolve infection without treatment. Tetracyclines are the drug of choice. Supportive therapy may include glucocorticoids at immunosuppressive doses. Metronidazole (40 mg/kg orally once daily for 3 weeks) has been used to treat resistant infections (Breitschwerdt, 1995).

ANAEROBIC INFECTIONS

Anaerobes differ from other bacteria in that they do not require the presence of molecular oxygen for metabolic activity and growth but depend on fermentative processes. Strict anaerobes cannot tolerate the presence of oxygen and few are clinically significant. Growth of *obligate* anaerobes depends on an environment characterized by reduced oxygen tension and low oxidation-reduction (redox) potential. Most clinically significant anaerobic organisms are obligate and include the genera *Fusobacterium, Bacteroides, Clostridium*, (selected species), *Peptostreptococcus* (enteric *Streptococcus*), and *Peptococcus*. Although *oxygen-tolerant* anaerobes cannot utilize oxygen, they can grow in its presence. Oxygen-tolerant organisms include *Clostridium perfringens* and *Propionibacterium*. Finally, *facultative* anaerobes are characterized by flexible oxygen requirements and can grow in the presence or absence of oxygen. Facultative anaerobes, which are clinically important in small animals, include *Staphylococcus* and the enteric gram-negative bacilli such as *E. coli* and *Klebsiella* and *Pasteurella* species. (Dow et al., 1986; Dow and Jones, 1987). Like aerobic organisms, anaerobic organisms are also classified by their gram-staining characteristics. Gram-positive cocci include *Peptococcus* and *Peptostreptococcus*. Gram-positive rods include those that form spores (*Clostridium*) and those that do not (*Actinomyces* and *Propionibacterium*). Gram-negative anaerobic rods include *Bacteroides* and *Fusobacterium*.

The prevalence and significance of anaerobic infections in veterinary medicine have only been realized within the last decade. Results of studies investigating the incidence of anaerobic organisms as causative agents of infections in veterinary medicine have been relatively consistent. The most frequently isolated organisms in a recent study (Jang, 1997) were *Bacteroides, Peptostreptococcus, Fusobacterium*, and *Porphyromonas*. These organisms represented 70% of the isolates. Other previously reported clinically significant isolates include *Clostridium, Propionibacterium, Actinomyces*, and *Peptococcus* (Dow and Jones, 1987). Some older studies suggest that *Clostridium* species are more commonly isolated, but this finding may reflect inappropriate culturing techniques or regional differences in prevalence of selected genera.

Pathogenesis

Anaerobic infections are endogenous in origin because the causative organisms are most commonly members of the normal bacterial flora that occur in surrounding uninfected tissues. The normal bacterial flora of the body are predominantly anaerobic. Anaerobic organisms are particularly prevalent on mucous membrane surfaces as exemplified by an anaerobic to aerobic ratio of 1000:1 in the large intestine (colon) and 10:1 in the oral cavity (Greene, 1990). Anaerobic organisms, and particularly *Bacteroides* species, are also prevalent in the female reproductive tract (vagina). Infections by anaerobic organisms usually require a break in the normal skin or mucosal defense barriers, thus allowing penetration and contamination, or a break in the host's immune defenses. Thus, certain areas of the body are more predisposed to the development of anaerobic infections. The most common sites of anaerobic infections reported in small animals are the oropharynx, skin (including bite wounds), respiratory tract, abdomen, reproductive tract, musculoskeletal system, and CNS. Anaerobic organisms are also causes of bacteremia.

Anaerobic bacteria, particularly gram-negative rods, are often considered serious pathogens because they are capable of producing toxins and enzymes, which enhance their pathogenicity. Both *Bacteroides* (especially *B. fragilis*) and *Fusobacterium* produce potent toxins that not only cause tissue necrosis but also enhance the spread of infection. *Bacteroides* species may also produce collagenase. Clostridial organisms also produce a variety of toxic compounds that, in addition to tissue necrosis, may cause hemolysis, disseminated intravascular coagulation, and renal failure (Dow et al., 1986). Several organisms produce compounds that destroy leukocytes, thus debilitating a component of the host's immune system (Dow et al., 1986).

Diagnosis of anaerobic infections is often difficult. *Bacteroides* and *Fusobacterium* are often difficult to visualize in Gram stains when in the presence of exudates and tissue debris. Gram-positive organisms may appear gram-negative, or they may assume usual morphology in older exudates or following antibacterial therapy (Dow et al., 1986). Improper culturing techniques are probably the most common cause for failure to isolate all infective organisms (Hirsch et al., 1985; Dow et al., 1986).

Anaerobic infections should be suspected when an infection is characterized by one or more of the following: close proximity to a mucous membrane; a putrid, foul-smelling exudate; necrotic or gangrenous tissue; gas; a blackish discoloration of tissues (which may fluoresce under ultraviolet light if caused by *B. melaninogenicus*); sulfur granules (indicating infection caused by *Actinomyces*); a subacute onset of inflammation; and leukocytosis associated with a high fever (Dow, 1986; Finegold, 1995). Anaerobic infections also should be suspected when cultures are negative despite observation of organisms with a Gram stain and in cases of endocarditis associated with negative blood cultures. Closed-space infections such as pyothorax, pyometra, and brain, lung, or intra-abdominal abscesses are frequently caused by anaerobic infections. Other infections commonly caused by anaerobes include aspiration pneumonia, peritonitis associated with bowel contamination, chronic osteomyelitis associated with open fractures, bite wounds, penetrating foreign bodies, and solid tumors.

Factors Impacting Selection of Antimicrobials

Factors that contribute to therapeutic (antimicrobial) failure for anaerobic infections include improper culturing techniques, mixed infections, and inactivation of the antimicrobial. A common cause for therapeutic failure when treating bacterial infections is selection of an inappropriate antimicrobial drug. Culture and susceptibility information is vital for the proper management of anaerobic infections. Failure to isolate anaerobic organisms due to improper culturing techniques should be suspected whenever routine aerobic cultures of purulent exudate yield no growth.

Most clinically significant anaerobes are obligate and thus cannot survive exposure to oxygen for more than a few seconds. In addition, facultative bacteria generally grow faster than anaerobic organisms and thus may overgrow and mask anaerobic organisms, particularly if specimen culturing is delayed (Dow et al., 1986). The best specimens for anaerobic culture are aspirates or tissue biopsy specimens (1 cm^2) rather than swabs (Dow et al., 1989a, b). Suitable aspirates include those of infected body fluids (i.e., peritoneal, pericardial, pleural), aspirates of pus (from abscesses, deep wounds, or pyometra), tracheal or percutaneous lung aspirates, surgical tissue specimens (including samples from deep infections, bone biopsy material, or sequestra) and blood (Dow et al., 1989a, b). All air or gas bubbles should be removed from both the needle and syringe immediately after sample collection (Finegold, 1995). Urine; swabs for the oropharynx, upper airway, external airway, and reproductive tract; sputum or nasal exudates; and bronchoscopy brushings or aspirates (unless obtained with a double-lumen sleeve) are generally considered inappropriate. Culture samples should be placed in culture tubes (Finegold, 1995). Specialized transport receptacles should be devoid of oxygen and contain anaerobic media that will also allow isolation of aerobic organisms. Specimens collected in plastic syringes should also be placed in transport tubes because oxygen can slowly permeate through the syringe. Specimens generally should be kept at room temperature until transported.

Many anaerobic infections are caused by more than one organism. Both anaerobic/anaerobic and anaerobic/aerobic mixed infections have been reported in small animals. A mean of 1.7 to 1.9 anaerobic organisms were isolated per specimen in several studies. Samples usually also contained facultative anaerobes (Hirsch et al., 1979, 1985). A recent study cited 80% of infections with obligate anaerobes to simultaneously contain facultative anaerobic or aerobic organisms, with members of the family Enterobacteriaceae being the most common organisms isolated (Jang, 1997). These include *E. coli* followed by *Pasteurella* species and *Staphylococcus intermedius*. Mixed bacterial infections are often more virulent than infections caused by single organisms (Dow et al., 1986). Because synergistic mechanisms develop between facultative and anaerobic organisms, infection by multiple organisms may promote the overgrowth of commensal anaerobes such as *Actinomyces* (Hardie et al., 1983; Dow and Jones, 1987; Brook, 1995). *Bacteroides* species can inhibit phagocytic activity of surrounding white blood cells when present in mixed infections. Commensal bacteria may act as symbiotes by producing growth factors required by pathogenic anaerobic organisms. Facultative organisms may also provide a more favorable environment for anaerobes by removing oxygen and adding reducing substances (Dow and Jones, 1987). The number of microorganisms located within an abscess may also have an effect on drug efficacy because antimicrobial inactivation is more likely.

The environmental conditions surrounding an anaerobic infection can be detrimental to the activity of antimicrobial drugs. These effects, discussed in Chapter 8, are very likely to be marked in some anaerobic infections. The inflammatory exudate that usually accompanies anaerobic infections can have profound effects on drug efficacy. Cellular membranes, breakdown products of phagocytic cells, and inflamed tissues are all capable of binding to and reducing the effective concentration of pharmacologically active antimicrobial drugs (Levin and Karakusis, 1984). Host tissues may also produce local enzymes that destroy antibiotics (Levin and Karakusis, 1984).

The anaerobic environment that characterizes anaerobic infections can also profoundly alter the efficacy of antimicrobials. The *oxidation-reduction potential* (referred to as EH), which measures the anaerobiosis associated with an abscess, is estimated to be approximately −400 mV in human abscess, which is indicative of an environment free of oxygen. The lack of oxygen has profound effects on two activities important to the success of antimicrobial therapy. The first is its effect on white blood cells. To kill selective organisms, white blood cells must be able to initiate oxidative bursts, an activity that is very difficult to accomplish in the anaerobic environment (Tally, 1988; Tally and Cuchural, 1988). In addition, white blood cell chemotaxis in response to bacterial factors is reduced in anaerobic environments (Finegold, 1995). The second detrimental effect an anaerobic environment has on the activity of certain antimicrobial drugs relates to the mechanism of transport or action of the drugs. The efficacy of aminoglycosides and the combination of trimethoprim/sulfamethoxazole are particularly affected. Aminoglycosides require active transport into cells by mechanisms dependent on oxygen. In addition, the mechanism of action of these antimicrobials depends, in part, on cellular respiration processes that utilize oxygen. The lack of oxygen renders these antibiotics ineffective; all anaerobic organisms are thus resistant to aminoglycosides. The aerobic component of a mixed infection may also be resistant to aminoglycoside therapy because the oxidative transport systems of such organisms (e.g., *E. coli*) may shut down in an anaerobic environment.

The development of resistance by anaerobic organisms to selected antimicrobials is an important cause of therapeutic failure. As with other bacteria, plasmid-mediated, transferable drug resistance and the inability of drugs to penetrate bacterial cells are important mechanisms by which anaerobic organisms develop resistance to antimicrobials (Finegold, 1995). Several studies have concentrated on the development of resistance to β-lactam antibiotics. Anaerobic organisms, and particularly *B. fragilis*, develop resistance to these drugs primarily by blocking all penetration by the drug or by producing β-lactamase enzymes that inactivate the drug. *Bacteroides fragilis* is particularly adept at developing resistance due to the production of β-lactamases (penicillinases or cephalosporinases), enzymes that cleave the β-lactam ring, thus effectively destroying antimicrobial activity. Most strains of *B. fragilis* produce a chromosomally mediated β-lactamase, which inactivates many cephalosporins, particularly first-generation drugs. In addition to this cephalosporinase, many strains of *B. fragilis* can acquire novel β-lactamases that are characterized by greater efficacy against the penicillins than the cephalosporins. One study found that some strains of *B. fragilis* could produce β-lactamases that are capable of inactivating cefoxitin and imipenem, two drugs that historically have been effective for the treatment of anaerobic infections (Tally and Cuchural, 1988). Several of these strains are, however, capable of producing massive quantities of the cephalosporinase. Although this enzyme does not have much specific activity against cefoxitin, the drug is inactivated because of the vast quantities produced. Cefoxitin resistance of this nature can be transferred to other strains of *Bacteroides*. A study that investigated the emerging resistance patterns of *B. fragilis* to various antimicrobial agents over a 3-year period found that resistance to cefoxitin, originally the most active drug against this species, doubled in 2 years.

Bacteroides species also possess a sophisticated system of resistance by which they transfer to both clindamycin and tetracycline. In the above-mentioned 3-year study, resistance to clindamycin did not increase, and no organisms were resistant to metronidazole or chloramphenicol. Although tetracyclines were the drug of choice for infections caused by *B. fragilis* in the early 1950s, almost 66% of the organisms were resistant to the drug. Variation in anaerobic (e.g., *B. fragilis*) resistance patterns have been described for different geographic regions. In addition, various patterns have been described based on site of tissue or sample collection. One study found that organisms isolated from the blood were more resistant to piperacillin, cefoxitin, and clindamycin than were the same isolated obtained from the abdominal cavity. Experimental studies have shown that resistance genes can be naturally transferred from *B. fragilis* to *E. coli*. This finding may have profound implications for the treatment of mixed anaerobic/aerobic infections, particularly those originating from colonic bacteria. A recent study (Jang, 1997) has documented a 29% incidence of resistance of *Bacteroides* to ampicillin; in contrast, 100% were susceptible to amoxicillin, clavulanic acid, and chloramphenicol, and most were susceptible to metronidazole. Only 83% were susceptible to clindamycin.

Antimicrobial Drugs

The successful treatment of an anaerobic infection depends on altering the local environment in a manner designed to reduce bacterial proliferation and checking the spread of infection into adjacent tissues. The first goal is achieved by surgical débridement of dead tissue. At the time of surgery, pockets of pus should be drained, trapped gas released, and any obstructions to drainage eliminated. Surgery should also improve circulation to the site of infection, which will improve oxygenation of tissues. Local spread of infection is managed by administration of an antimicrobial. Although the number of antimicrobials that can be used to treat anaerobic infections is limited, there are several that are effective and safe.

β-Lactam Antibiotics

Penicillin G, a natural antibiotic, is the prototype penicillin. The anaerobic susceptibility of the semisynthetic aminopenicillins ampicillin and amoxicillin is similar to that of penicillin G. In contrast to penicillin G, they are effective after oral administration. Penicillins are the drug of choice for clostridial infections and for *Peptostreptococcus*. They are generally effective against *Fusobacterium* and *Actinomyces*. Although the penicillins are effective against many *Bacteroides* species, several species, including *B. melaninogenicus* and *B. fragilis*, both of which are clinically important, are uniformly resistant to most penicillins (Dow, 1986) with the exception of piperacillin (Tally, 1988). A 33% rate of resistance by *Bacteroides* species to penicillin G has been reported in veterinary patients. A large percentage of these strains were also resistant to ampicillin and cephalothin (Hirsch et al., 1985). Jang (1997) reports that 29% of *Bacteroides* isolates in veterinary medicine are resistant to ampicillin. The efficacy of penicillin (and cephalosporin) antibiotics against *B. fragilis* can be improved by combining the antibiotic with clavulanic acid or sulbactam. Indeed, Jang (1997) reported all *Bacteroides* isolates to be susceptible to amoxicillin-clavulanic acid. Both of these drugs have a greater affinity for β-lactamases than do the β-lactam antibiotics and preferentially bind to and inactivate the bacterial enzyme. The efficacy of amoxicillin against *B. fragilis* is greatly enhanced when combined with clavulanic acid (Indiviri and Hirsch, 1985). The addition of clavulanic acid also enhances the efficacy of amoxicillin against several gram-negative enteric organisms, which may be important factors in the pathogenesis of mixed infections. Jang (1997) found 100% of clostridial organisms to be susceptible to ampicillin compared to 80% of isolates that were susceptible to clindamycin.

The cephalosporins are very similar to the penicillins in pharmacokinetic characteristics but may be less efficacious against anaerobes. First-generation cephalosporins (e.g., cephalothin, cefazolin, and cefadroxil) may be effective against many anaerobic organisms, with the exception of *B. fragilis.* The second-generation cephalosporin cefoxitin is, however, one of the most effective antibiotics against anaerobic infections, including *B. fragilis*, although resistance is increasing as was previously noted. As a second-generation cephalosporin, cefoxitin is also effective against many gram-negative enteric organisms, which enhances its utility for the treatment of mixed infections. Many *Clostridium* species are resistant to most cephalosporins; thus alternative antimicrobials should be considered for infections caused by these organisms. Currently, piperacillin and cefoxitin remain the most active β-lactam antibiotics for the treatment of human anaerobic infections. Because of the variable nature of susceptibility patterns and the unique mechanisms and characteristics of β-lactams exhibited by anaerobic bacteria, however, culture and susceptibility monitoring of these pathogens in crucial. The carbapenems are the newest class of β-lactam antibiotics. Although their use is limited in veterinary patients, imipenem has been shown to be effective against most species of clinically significant bacteria, and it is one of the most effective β-lactam antibiotics against anaerobic infections.

Other Antimicrobials

Chloramphenicol is one of the most effective antimicrobial drugs against all strains of anaerobic bacteria, including penicillin-resistant *B. fragilis* (Jang, 1997). Its utility, however, is decreased by its bacteriostatic nature as well as by its tendency to cause adverse reactions, particularly in the cat, and concerns regarding human exposure. Clindamycin is a lincosamide antibiotic whose mechanism of action is similar to chloramphenicol. Like chloramphenicol, it is bacteriostatic against anaerobic organisms. Clindamycin is more efficacious for the treatment of anaerobic infections than its parent drug, lincomycin. Clindamycin is also concentrated in white blood cells at the site of infection, which is considered to be an important factor in the efficacy of this drug. This is an active, energy process, however, which may not occur in the oxygen-deficient environments that characterize anaerobic infections. The spectrum of activity of clindamycin includes anaerobic organisms. It is generally very effective against most strains (83% cited by Jang, 1997) of *B. fragilis,* including those resistant to penicillin and is very effective against veterinary isolates of *Clostridium.* Clindamycin is not, however, effective against *Clostridium difficile,* and its use may be associated with pseudomembranitis or other gastrointestinal disorders related to microbial overgrowth. *Clostridium difficile* may massively increase its exotoxin production in the gastrointestinal tract in the presence of subinhibitory plasma clindamycin concentrations due to increased bacterial synthesis of exotoxin (Atkinson and Lorian, 1998). The use of metronidazole, a popular antigiardial drug, for the treatment of anaerobic infections in dogs and cats has markedly increased. The drug is consistently effective against most anaerobes, including *B. fragilis* as well as most other strains of *Bacteroides.* Metronidazole is also effective for treatment of human cases of *C. difficile.* It is generally not effective against *Actinomyces* or *Propionibacterium.* Its mode of action probably results from disruption of bacterial DNA after bacterial metabolism to toxic metabolites. The low oxidation-reduction potential of the anaerobic environment is conducive to bacterial formation of toxic metabolites.

Vancomycin is the drug of choice for humans for the treatment of antibiotic-associated colitis caused by *C. difficile.* Its mechanism of action results from inhibition of bacterial cell wall synthesis. Thus, its actions are primarily bactericidal. Its spectrum includes *Clostridium,* gram-positive bacilli (*Bacillus, Actinomyces*), and *Propionibacterium.*

The sulfonamides can be effective against many anaerobic organisms. Caution should be taken, however, because of the patterns of resistance that have been noted for veterinary anaerobic isolates. For serious or difficult anaerobic infections, sulfonamide use should be based on susceptibility data.

SELECTED ANAEROBIC INFECTIONS

Clostridum tetani

Tetanus is caused by the neurotoxin tetanospasmin produced by vegetative *Clostridum tetani*, a motile, gram-positive spore-forming anaerobe (Greene, 1998d). Spores contaminating an anaerobic site (e.g., in the presence of a foreign body or tissue necrosis) vegetate. The toxin enters axons of local motor neurons, and by retrograde movement reaches the axonal body in the spinal cord. Eventually the toxin reaches the brain, where it inhibits the release of inhibitory neurotransmitters gamma-amino butyric acid and glycine, resulting in presynaptic blockade for selected synapses of the spinal cord (predominant site) and brain. Clinical signs generally occur within 5 to 10 days of wound acquisition, although delays of up to 3 weeks have been reported. Wounds closer to the head are associated with more rapid onset of generalized tetanus. Relative resistance of carnivores to the toxin may result in signs localized to the wound area, manifested as stiffness that usually spreads to the opposite limb or beyond. Generalized tetanus is characterized as extreme muscle rigidity, manifested as a stiff gait, difficulty in standing or lying down, and hyperthermia. Intracranial signs accompany localized tetanus, resulting in hypertonic facial muscles (e.g., trismus or lockjaw) and reflex muscle spasms. Animals have difficulty with prehension or swallowing solid food. Dysuria, urine retention, constipation, and gas distention are not unusual. Death, when it occurs, usually results from respiratory compromise (Greene, 1998d). Untreated cases can prove fatal, although natural resistance often limits the disease to localized or mild cases.

Treatment focuses on antimicrobial therapy in an attempt to decrease formation of neurotoxin and neutralization with antitoxin of any toxin not yet bound to nerve tissue. Recovery is slow and progressive, even when antitoxin is administered. The IV route is preferred to the IM or SC routes (the latter may require 48 to 72 hours for therapeutic concentrations to be reached). Antitoxin (<20,000 U) should be administered every 5 to 10 minutes; the dose should be decreased for larger dogs. Pretreatment of anaphylaxis is appropriate; administration of a test dose (0.1 to 0.2 mL) SC or ID may help identify those at risk (formation of a wheal at the site). Localized injection at the wound site (1000 U) may be helpful; likewise, intrathecal injection has been shown experimentally to reduce morbidity and mortality in dogs, probably because of better access to neurotoxin bound to nervous tissue. Local and systemic antibiotic therapy should be used to eradicate vegetative clostridial organisms, thus reducing the amount of toxin released. Metronidazole is superior to penicillin G and tetracyclines.

Supportive therapy for tetanus includes control of reflex spasms or convulsions. Phenothiazines (chlorpromazine preferred) combined with barbiturates (pentobarbital or phenobarbital) have been recommended as the preferred treatment (Greene, 1998d). Caution with the use of phenothiazines is recommended for patients with seizures; phenothiazines lower seizure threshold and can worsen seizures associated with other disorders. Phenobarbital should be administered as a loading dose (12 mg/kg to achieve the lower end of the recommended range for epilepsy). Glycopyrrolate should be administered to control bradycardia that may occur with the combined use of these drugs. Benzodiapines (diazepam) may be useful for controlling spasms and hyperexcitability; methocarbamol is a less effective centrally acting skeletal muscle relaxant. Dantrolene, a peripherally acting skeletal muscle relaxant, may be useful for the control of spasticity. Tetanus-induced respiratory compromise requires intubation and respiratory support.

Clostridium botulinum

Botulism in dogs is almost exclusively caused by type C *Clostridium botulinum* organisms that release the neurotoxin in a vegetative state (Barsanti, 1998). Although released in the inert form, cleavage by tissue or bacterial proteinases generates the dichain metalloproteinase neurotoxin, which is similar to tetanus toxin. Generally, clinical signs result from ingestion of the preformed toxin in part because adult animals generally are resistant to colonization by the organism, although antimicrobial therapy can facilitate colonization. The toxin is absorbed by intestinal lymphatics as with nutrient proteins; toxin complexed with other proteins appears to protect the toxin from intestinal degradation. At the nerve terminal, the toxin prevents the presynaptic release of acetylcholine by irreversibly binding. The toxin is characterized by a very high affinity for the presynaptic membrane receptors, making it one of the most potent toxins. At this point, the toxin is susceptible to inactivation by antitoxin. However, once receptor-mediated endocytosis has moved the toxin into the cell, antitoxin activation can no longer occur. Of the two chains, the L chain is more likely to inhibit acetylcholine release. Clinical sequelae, evident within hours but delayed for up to 6 days, include paralysis and degeneration of the affected synapse with subsequent lower motor neuron and parasympathetic dysfunction. Death generally does not occur unless paralysis extends to the respiratory tract. Recovery follows formation of new terminal axons and neuromuscular junctions with cranial nerve, neck, and forelimb functions generally returning to normal first.

Therapy focuses on supportive care; spontaneous recovery generally will occur in all animals if respiratory function is not impacted. Antitoxin is ineffective if nerve endings have been penetrated, which generally occurs rapidly; however, treatment may be beneficial if oral absorption of the toxin is ongoing. Type C antitoxin (10,000 to 15,000 U, IV or IM) should be administered twice, 4 hours apart. The antitoxin remains in the system for 40 days, mitigating the need for follow-up therapy. Penicillin or metronidazole can be administered to reduce the intestinal growth of *C. botulinim*, although the efficacy of this practice is questionable and may be contraindicated if organism death is thought to increase toxin release. Neuromuscular potentiators (aminopyridine, diaminopyridine, guanidine hydrochloride) have not proved effective.

Clostridium perfringens

C. perfringens capable of producing an enterotoxin can cause severe diarrhea (Greene, 1998e). Binding of the toxin to intestinal epithelial cells increases permeability, causing fluid and ion secretion, cell death, and sloughing of the intestinal mucosa. Sporulation leading to enterointoxication can occur following antimicrobial therapy, increased intestinal pH, dietary alteration, immunosuppression or associated with viral enteritis. Enterotoxemia can cause rapid death. Very occasionally, clinical signs may occur following ingestion of contaminated meat or as a result of nosocomial infections. Therapy includes antimicrobials and intensive fluid therapy. Antimicrobials that are variably effective include metronidazole, ampicillin, amoxicillin-clavulanic acid, tylosin, clindamycin, or tetracyclines.

ANTIMICROBIAL PROPHYLAXIS

The prophylactic use of antibiotics must be distinguished from treatment. The presence of infection, or anticipated infection after bacterial contamination (i.e., a compound fracture; contamination of abdominal contents with intestinal fluid), indicates the need for treatment rather than prophylaxis. If antimicrobial prophylaxis is to be implemented in anticipation of an invasive procedure (e.g., surgery), the following should serve as a basis for selection: The antimicrobial should target the most likely pathogenic organism; adequate concentrations of drug should be at the site of invasion before potential contamination; the antimicrobial should either have a long elimination half-life or be redosed during lengthy procedures; the least toxic drug should be selected; and the duration of therapy should be as short as possible (Schimpff et al., 1989; Neu, 1994).

Prophylactic therapy should not be used indiscriminantly in the immunocompromised animal. The granulocytopenic patient is particularly predisposed to the development of suprainfection. Suprainfection occurs in 10% to 20% of human granulocytopenic patients receiving empirical broad-spectrum antimicrobials. Prolonging therapy increases the chance that suprainfection will occur (Schimpff et al., 1989). Prophylactic suppression of gastrointestinal flora is recommended in human patients who are profoundly granulocytopenic for more than 2 weeks. Traditional use of nonabsorbable antimicrobials effective against aerobic gram-negative organisms (e.g., neomycin), and drugs that target anaerobic organisms (e.g., metronidazole), are being replaced by use of trimethoprim/sulfonamide combinations or fluorinated quinolones (Schimpff et al., 1989). Trimethoprim/sulfonamide combinations are more palatable and less expensive, yet they are equally effective in preventing infections when compared with more expensive drugs in human critically ill patients. Fluorinated quinolones allow persistence of anaerobic organisms in the gastrointestinal tract, thus reducing overgrowth of resistant gram-negative organisms and preventing rapid repopulation and overgrowth of aerobic gram-negative organisms as the antimicrobial is discontinued.

Other indications for medical prophylaxis include dentistry and prevention of recurrent, chronic infections (e.g., urinary tract and skin). The use of antibiotics prophylactically for these conditions is discussed separately in the corresponding chapter.

SURGICAL PROPHYLAXIS*

Antimicrobial prophylaxis is defined as the administration of an antimicrobial agent in the absence of infection. The aim of prophylactic therapy is to reduce the number of viable bacteria present in the surgical wound to a level that normal host defenses can handle, thus preventing infection. Contaminating bacteria can enter the surgical wound from exogenous sources or the patient's endogenous flora. Exogenous sources include surgical equipment, the surgery room, and surgical personnel. Duration of the surgical procedure plays a role in the incidence of wound infections, especially for procedures that last longer than 90 minutes.

Endogenous sources probably play a greater role in postoperative infections than exogenous sources. Endogenous sources include skin and mucosal surfaces that are transected during surgery. Hematogenous spread of bacteria may result from overt or occult septic foci or dental manipulations. Such sources should be either eliminated before surgery by appropriate therapeutic antimicrobial agents or avoided by not combining dental manipulations with surgery of body cavities (abdominal or thoracic) or orthopedic procedures.

Antimicrobial prophylaxis is not a substitute for good surgical technique, including aseptic technique and gentle tissue handling. Considerations in the use of antimicrobial prophylaxis are the type of surgery, potential pathogens encountered, host competence, and pharmacologic and antibacterial properties of the antimicrobial agent.

Type of Surgery

Surgical wounds are classified as clean, clean-contaminated, contaminated, or dirty. Clean wounds are made under aseptic conditions, are closed primarily, and are not drained. Prophylactic antimicrobial therapy is not warranted for most clean procedures, because bacterial contamination is minor, and the patient's competence helps prevent wound infection. Possible indications for the use of antimicrobials in clean surgical procedures are when the consequences of infection would be catastrophic (e.g., total joint replacement) or when surgical implants are used.

Clean-contaminated wounds include those made in the gastrointestinal, genitourinary, or respiratory tract without significant intraoperative spillage. Also, clean procedures in which a major break in sterile procedure occurred are considered clean-contaminated. Clean-contaminated wounds may benefit from prophylactic antibiotic therapy, and consideration of the following factors seems appropriate when contemplating the use of perioperative antimicrobial therapy: numbers of resident bacteria encountered, amount of spillage expected, and impact of disease condition on bacterial colonization. Resident bacterial numbers vary depending on the site of the tract incised and the nature of disease. In the normal gastrointestinal tract, resident bacteria are numerous in the oropharyngeal cavity, distal ileum, and colon. Numbers are normally much lower in the distal esophagus, stomach, and most of the small intestine. The genitourinary tract above the distal urethra has low bacterial populations, normally. The normal trachea and bronchi also have relatively sparse flora. Although amount of spillage cannot always be predicted preoperatively, prophylactic antibiotics are probably indicated if the risk of intraoperative spillage seems high. Diseases, in general, tend to modify both bacterial numbers (usually increased numbers) and populations (usually more virulent forms).

Contaminated wounds include those in which there is acute, nonpurulent inflammation or those in which gross contamination from a hollow viscus occurs. Antimicrobial prophylaxis is generally warranted when surgery is performed on contaminated wounds. Also, the presence of extensive tissue damage or accumulation of blood within wounds may warrant prophylactic drug administration because bacterial colonization is usually promoted.

Dirty or infected wounds benefit from irrigation with antiseptics. Chlorhexidine (0.05%) is an effective wound disinfectant for infected wounds. Use of antimicrobials (systemically, topically, or both) is generally indicated before surgery to treat an infected or dirty wound. Such use is more appropriately termed *therapeutic antimicrobial therapy.*

Potential Pathogens Encountered

The most frequently encountered pathogenic bacterial contaminants of surgical wounds are *Staphylococcus* species and *E. coli.* The most common skin bacteria are *Staphylococcus* species, although many other organisms may be present as transient, topical flora. The oropharynx has a mixed population of gram-positive organisms (especially *Staphylococcus* species, *Streptococcus* species, and *Actinomyces pyogenes*), gram-negative organisms (*Proteus, Pasteurella,* and *Pseudomonas* species and *E. coli*), and anaerobic organisms. The stomach and small intestine have very few organisms normally present, while the distal ileum and large intestine have large numbers of gram-negative (especially *E. coli* and *Klebsiella, Pseudomonas,* and *Salmonella* species) and anaerobic organisms. Potential pathogens encountered in the genitourinary tract include both gram-positive and gram-negative organisms (especially *Staphylococcus* and *Streptococcus* species, *E. coli,* and *Proteus* and *Pseudomonas* species). Pathogens of the respiratory tract (especially lower respiratory tract) include both gram-positive organisms (*Staphylococcus* and *Streptococcus* species and *A. pyogenes*) and gram-negative organisms (*Pseudomonas* species, *E. coli*, and *Klebsiella, Pasteurella,* and *Enterobacter* species).

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*Contributed by Harry W. Boothe, Texas A&M University.

Host Competence

Host resistence may be compromised systemically or locally. Patients with systemic immunodeficiency often have chronic, recurrent, or partially responsive infections. Prophylactic antimicrobial therapy is probably indicated for such patients regardless of the surgical procedure to be performed. Secondary immunodeficiencies have been associated with a variety of diseases, including hepatic or renal failure, hyperadrenocorticism, diabetes mellitus, and neoplasia. Other factors that may impact systemic host competence include advanced age, severe malnutrition, obesity, immunosuppressive drugs, and splenectomy.

Local factors of importance in the maintenance of host competence include tissue perfusion and tissue trauma. Competency of local defense mechanisms may be affected adversely by obstruction, neoplasia, ulceration, and hemorrhage. For example, the bacterial flora of a stagnant loop of jejunum caused by intestinal obstruction resembles that of the normal distal ileum (i.e., large numbers of resident bacteria). For the purposes of selecting perioperative antimicrobials, the clinician should accurately assess host competence before the surgical procedure.

Pharmacologic and Antibacterial Properties

The primary goal to be achieved by administration of prophylactic antimicrobial agents is to produce adequate concentrations of antibiotic at the surgical incision site at the time of wound contamination. Also important is the concept that the major risk of contamination is at the time of surgery until a fibrin seal develops between wound edges (approximately 3 to 5 hours postoperatively). Factors of importance to the use of perioperative antimicrobials are absorption (timing and route of administration), distribution, and elimination characteristics. Absorption issues are of least concern with intravenously administered antibiotics. For most antibiotics, distribution is relatively rapid and complete within 30 to 60 minutes after intravenous administration. The concentration of drug achieved in the tissue correlates with the concentration of free drug in the serum. Highly protein-bound drugs (i.e., little free drug in the serum) achieve lower tissue concentrations than do weakly bound agents (e.g., cefazolin, gentamicin, and ampicillin). Other factors such as lipid solubility, pH, and local environment may also influence tissue penetration of the drug. Elimination of most antibiotics is principally via the kidneys. The rate of elimination determines what dosing interval is selected. More rapidly eliminated drugs require more frequent administration. Cefazolin, for example, should be administered at 2-hour intervals during the surgical procedure to maintain adequate tissue and serum levels.

The following prophylactic antibiotic regimen seems appropriate: an intravenous bolus of drug given 30 to 60 minutes before incision (i.e., at anesthetic induction) and another bolus of drug given at the completion of the procedure. If the surgical procedure lasts longer than 3 hours, an additional intraoperative dose of antibiotic should be given approximately 2 to 3 hours after the initial dose. There is no rationale for continuing antibiotic administration longer than 24 hours after surgery in the absence of documented infection. If infection is documented, then therapeutic antimicrobial therapy is initiated.

The selected drug should be bactericidal for the pathogens that are most likely to contaminate the surgical site. First-generation cephalosporins (e.g., cefazolin) are generally as effective and less expensive than second-generation and third-generation ones. Surgery of the lower gastrointestinal tract may require a more elaborate schedule of prophylactic drug administration. A second-generation cephalosporin (e.g., cefoxitin) or an aminoglycoside/anaerobic combination (e.g., amikacin and clindamycin or gentamicin and amoxicillin) should be administered systemically.

Inappropriate perioperative antimicrobial use has been shown to increase the incidence of complications. Examples of inappropriate perioperative antimicrobial use include use of antimicrobials for clean surgical procedures, initiation of prophylactic antimicrobials postoperatively, and continuation of antimicrobial administration for longer than 24 hours. Each of these actions risks the occurrence of one or more of the following complications: reduced efficacy, superinfection, selection of resistant bacterial pathogens, greater client cost, and a potential for higher incidence of drug-associated complications.

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11 Treatment of Fungal Infections

Dawn Merton Boothe

INTRODUCTION
POLYENE MACROLIDE ANTIBIOTICS: AMPHOTERICIN B
Structure-Activity Relationship
Mechanism of Action
Spectrum of Activity
Resistance
Pharmacokinetics
Preparations
Side Effects
Therapeutic Use
IMIDAZOLE DERIVATIVES
Structure-Activity Relationship
Mechanism of Action
Spectrum of Activity
Pharmacokinetics
Preparations
Drug Interactions and Side Effects
Therapeutic Use
FLUCYTOSINE
Structure-Activity Relationship
Mechanism of Action
Spectrum of Activity
Pharmacokinetics
Preparations
Side Effects
GRISEOFULVIN
Structure-Activity Relationship
Mechanism of Action
Spectrum of Activity
Pharmacokinetics
Preparations
Side Effects and Drug Interactions
ALLYLAMINES
IODIDES
THERAPEUTIC USE OF ANTIFUNGAL AGENTS
Topical Fungal Infections: Dermatophytosis
Yeast or Yeast-Like Infections
  Malassezia
  Candidiasis
Systemic Fungal Diseases
  Blastomycosis
  Histoplasmosis
  Cryptococcosis
  Coccidioidomycosis
  Aspergillosis
Subcutaneous Mycoses
  Sporotrichosis
  Rhinosporidiosis
  Pythiosis

INTRODUCTION

The pathogenic fungi affecting humans and animals are eukaryotes, generally existing as either filamentous molds (hyphal forms) or intracellular yeasts (Table 11–1) (McGinnis and Rinaldi, 1996). Dimorphic fungi grow in the host as a yeast-like form but as molds in vitro at room temperature. Some fungi (e.g., *Coccidioides immitis, Histoplasma,* and *Rhinosporidium* species) grow inside host cells, dividing into spores until released from the cell as it ruptures. Fungal infections differ from bacterial infections in several respects, and pathogenic fungi have developed several characteristics that complicate antimicrobial therapy (Bennett, 1990a and b). For example, *Cryptococcus* and occasionally *Sporothrix schenkii* produce an external coating or slime layer that encapsulates the cells and causes them to adhere and clump together (Carter and Chengappa, 1991). The fungal cell wall is rigid and contains chitin and polysaccharides, which generally precludes Gram staining and serves as a barrier to drug penetration. The cell membrane is complex and, unlike bacteria but as with higher eukaryotes, contains sterols (Carter and Chengappa, 1991). In contrast to bacteria, several fungal organisms do not produce exotoxins in vivo, and there is no conclusive evidence that fungi produce endotoxins.

Fungal organisms are characterized by a low invasiveness and virulence. In fact, most animals will overcome a fungal infection. Immunity to fungal organisms appears to be cell mediated, although all but dermatophytes also stimulate antibody production. Factors that predispose the patient to infection include necrotic tissue, a moist environment, and immunosuppression. Fungal infections can be primarily superficial and irritating (e.g., dermatophytosis) or systemic and life threatening (e.g., dimorphic fungal infections including blastomycosis, cryptococcosis, histoplasmosis, and coccidioidomycosis). Fungal organisms may exhibit an affinity for certain tissues, such as the dermatophytes for keratin and *Histoplasma capsulatum* for macrophages. Animals may develop a hypersensitivity to the infecting organism (as is often seen in dermatophyte infections), which can result in a pathologic response to the infection as well as facilitate dissemination. On the other hand, the lack of hypersensitivity may also indicate a poorer prognosis for recovery (Carter and Chengappa, 1991).

Several factors can lead to therapeutic failure or relapse after antifungal therapy (Graybill, 1990; Bennett, 1990b). In humans, relapsing infections are not uncommon for selected *Trichophyton* species and for invasive mycoses in immunocompromised patients. In the latter group, aspergillosis infections are particularly problematic. Several organisms, particularly the superficial pathogens and systemic opportunistic organisms, have a primary resistance to antifungal drugs. In some instances, therapeutic failure reflects poor penetration of drug into infected tissues (particularly the central nervous system and bone or into those organisms that are encapsulated). As with bacteria, the pattern of fungal disease is constantly changing. The advent of acquired immunodeficiency syndrome in human patients has been important to the development of new strains of resistant organisms, and there remains a continuing need for development of new antifungal agents. Finally, toxicity

Table 11–1. Grouping and Minimum Inhibitory Concentration Ranges (mg/mL) of Pathogenic Fungi

Organism	Amphotericin B	Ketoconazole	Itraconazole	Fluconazole	Clotrimazole	5-Flucytosine	Griseofulvin
Alternaria alternata							0.5
Aspergillus							
flavus	12.5–>25	0.5–10	0.063–0.13	Not available (NA)	0.5–2	10–>100	—
fumigatus	0.14–>25	0.12–25	0.001–10	NA	0.1–10	0.5–>100	—
niger	0.12 > 25	1–100			0.5–10		
Blastomyces dermatitidis	0.05–0.78	0.005–2	0.063-0.13	NA	0.13-3.13	0.06–>100	—
Candida albicans	0.04–4	0.01–>100	0.063–128	0.125–>80	0.01–50	0.016–100	>100
Coccidioides	0.15–96	0.05–0.64		NA	0.1–3.4	>97	—
Cryptococcus neoformans	0.04-2.8	0.063–32	0.001–0.5	NA	0.02–4	0.1–>100	—
Histoplasma capsulatum	0.0007–>100	0.063–3.12	0.063	NA	0.1–1	NA	—
Malassezia furfur	0.3–2.5	0.01–0.4	0.001–1	NA	0.2–12.5	>100	—
Microsporum canis	1.8	0.5–16	0.063–0.25*	NA	0.03–2	NA	0.1–>18
Microsporum gypseum	2.3	0.002–0.004		NA	0.1–2	NA	0.5–3.13
Sporothrix schenckii	0.4–>100	0.25–>64	0.001–4	NA	0.5–10	1.6–3.12	—
Trichophyton mentagrophytes	5.6	0.001–>64		NA	0.01–20	NA	0.1–>30
Trichophyton sp.	5.42 > 100	0.1–12.5	≤0.03–0.25	1–64	0.015–2	NA	0.1–>30

*Microsporum sp.

Data from McGinnis MR, Rinaldi MG: Antifungal drugs: mechanisms of action, drug resistance, susceptibility testing, and assays of activity in biological fluids. In Lorian V (ed): Antibiotics in Laboratory Medicine, 4th ed, pp 176–211. Baltimore, Williams & Wilkins, 1996.

of antifungals is a common cause of therapeutic failure. Because both the antifungal target organism and the host cells are eukaryotic, the cellular targets of fungal organisms are substantially different from those of bacterial organisms. As a result, antibacterials generally are ineffective against fungal organisms, and, in contrast to most antibacterials, antifungals are often toxic or associated with undesirable side effects in the host. The incidence of side effects has limited the number of effective, yet safe antifungal drugs available.

Unlike antibacterial therapy, antimicrobial culture and susceptibility testing has not been well developed as a tool for the treatment of fungal infections. In vitro susceptibility testing of antifungal agents is highly dependent on test conditions, and interlaboratory results vary markedly. Interpretation of culture and susceptibility data is limited by a lack of standardized testing methods. As with bacteria, the minimum inhibitory concentration (MIC) for a fungal organism is the concentration of the antifungal drug that inhibits the growth of the fungus under standardized conditions (see Table 11–1). The minimum lethal concentration is the concentration that kills the organisms (McGinnis and Rinaldi, 1996). Correlation between MIC and clinical response is poor, and assessment of antifungal agents appears to be best accomplished through efficacy studies in animal models. Fortunately, the need for fungal culture and susceptibility testing may not be as critical for fungal organisms as it is for bacterial organisms because, with the exception of 5-flucytosine, fungal development of resistance to antimicrobial therapy is not common (Grant and Clissold, 1989). Resistance is more likely with a rapidly growing organism exposed to high concentrations of an antifungal for a long period of time (McGinnis and Rinaldi, 1996). Mechanisms of resistance of fungal organisms are similar to those of bacterial organisms. The advent of newer antifungal agents and resistance among fungal organisms is, however, likely to cause in vitro testing of antifungals to become more important to therapeutic success.

The primary agents used to treat fungal infections are the polyene macrolides (amphotericin B as the prototype), the azoles (ketoconazole as the prototype), and the newer allylamine antifungals. Flucytosine has a role of lesser importance in the treatment of dimorphic fungal diseases, particularly in animals. Griseofulvin belongs to no "group" yet has an important place in the armamentarium against dermatophytosis. As recently as 1988, the treatment of systemic fungal infections in humans emphasized the use of amphotericin B, ketoconazole, and flucytosine. In the decade that followed, further development of the azole derivatives has led to a new age in the treatment of systemic fungal diseases. Currently, antifungal therapy is most effective when based on an understanding of the therapeutic ratio of the drug in the infection being treated. For amphotericin B, this ratio tends to be small because of its toxicity. The newer azole derivatives have proven to provide much of the efficacy of amphotericin B without its toxicity.

POLYENE MACROLIDE ANTIBIOTICS: AMPHOTERICIN B

Structure-Activity Relationship

Examples of polyene (i.e., multiple double bond; Fig. 11–1) antifungal drugs include amphotericin B, nystatin, and pimaricin. Each antibiotic is produced by a different species of *Streptomyces* (family Actinomyces). *Amphotericin B* was developed in the 1960s and was so successful in

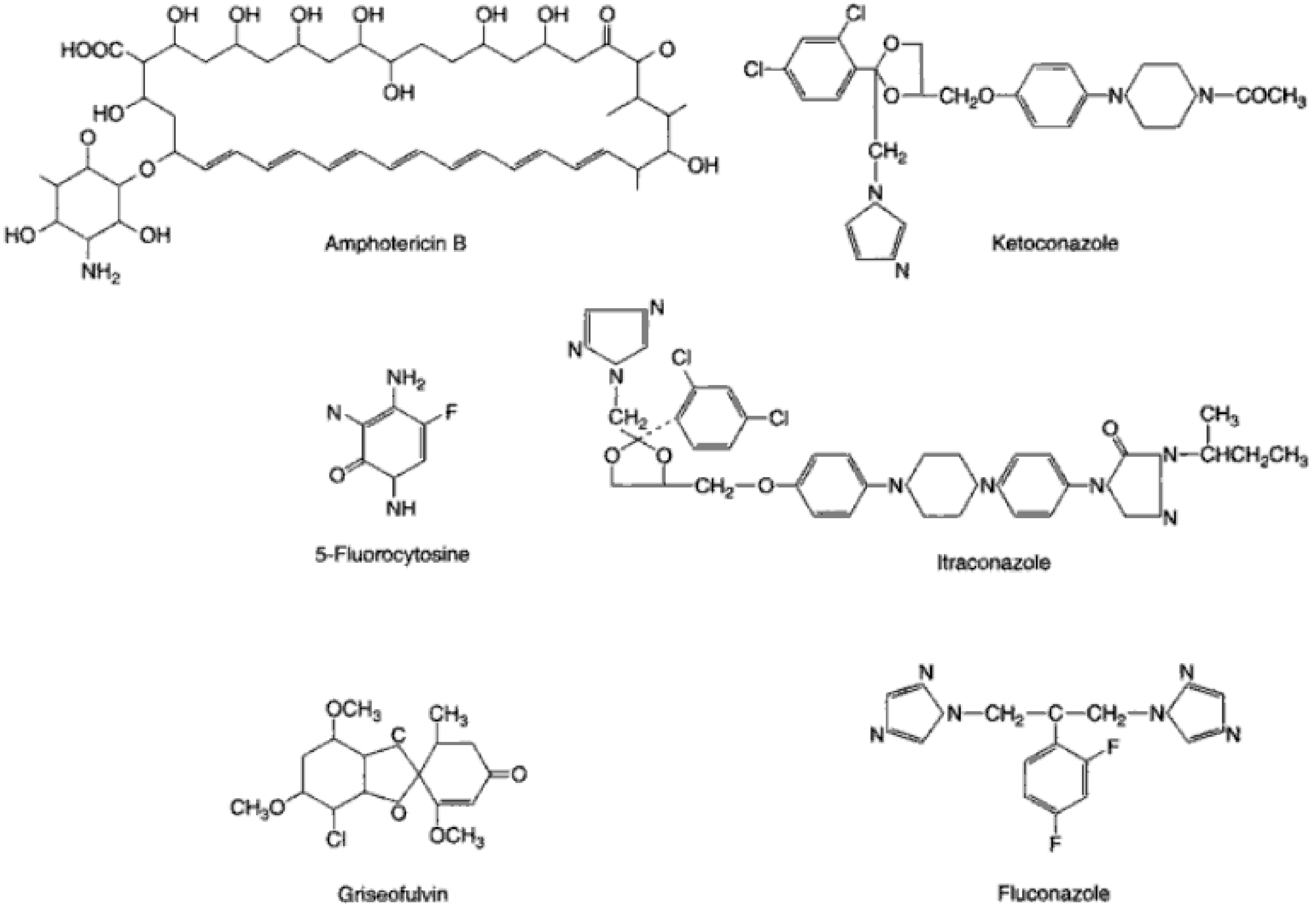

Figure 11–1. Chemical structures of selected antifungal drugs.

fulfilling the need for a broad-spectrum antifungal that further advancement of antifungal therapy was largely ignored. These drugs are very large molecules, consisting of a macrolide containing a large lactone ring. The polyene contains many double bonds and represents the lipophilic portion of the molecule. A hydroxylated hydrocarbon backbone represents the hydrophilic portion of the molecule. These compounds are insoluble in water and are unstable, and they will rapidly decompose if exposed to sunlight.

Mechanism of Action

Polyene macrolides bind with the sterol portion of the phospholipids comprising the fungal cell membrane. Amphotericin has a much higher affinity for *ergosterol*, the major sterol component of fungal cell membranes, than for cholesterol, the major sterol in mammalian cell membranes (McGinnis and Rinaldi, 1996). The interaction of the drug and the sterol results in the formation of channels or pores in the cell membrane. The result is an increase in cell permeability. Altered K^+/H^+ exchange results in the loss of K^+ and Mg^{2+} from the cell. Cellular metabolism is disrupted; internal acidification of the fungal cell and the loss of important organic molecules from the cell result in irreversible cell damage (Fig. 11–2). The efficacy of some of the drugs can be related to their ability to bind to ergosterol. Amphotericin is fungistatic but can be fungicidal at high concentrations. At high concentrations, the drug directly disrupts the fungal cell membrane. As with some other select antifungal drugs, amphotericin appears to have some immunomodulating characteristics. Both humoral and cell-mediated immunity may be enhanced, thus increasing the host's ability to overcome infection.

Spectrum of Activity

Despite the advent of the azole antifungal drugs, amphotericin B remains the most effective agent against most of the major fungal pathogens. The indications for amphotericin therapy include most systemic fungal diseases including those caused by the dimorphic fungi (histoplasmosis, blastomycosis, cryptococcosis, and coccidioidomycosis) and disseminated sporotrichosis, phycomycosis, aspergillosis, and candidiasis. Amphotericin B has greater activity against some organisms (e.g., *Candida* and *Aspergillus* species and coccidioidal meningitis) than the newer azoles and particularly fluconazole. Amphotericin B is not effective against dermatophytes.

Resistance

The incidence of resistance to amphotericin B is low and has been documented primarily for *Candida*. The develop-

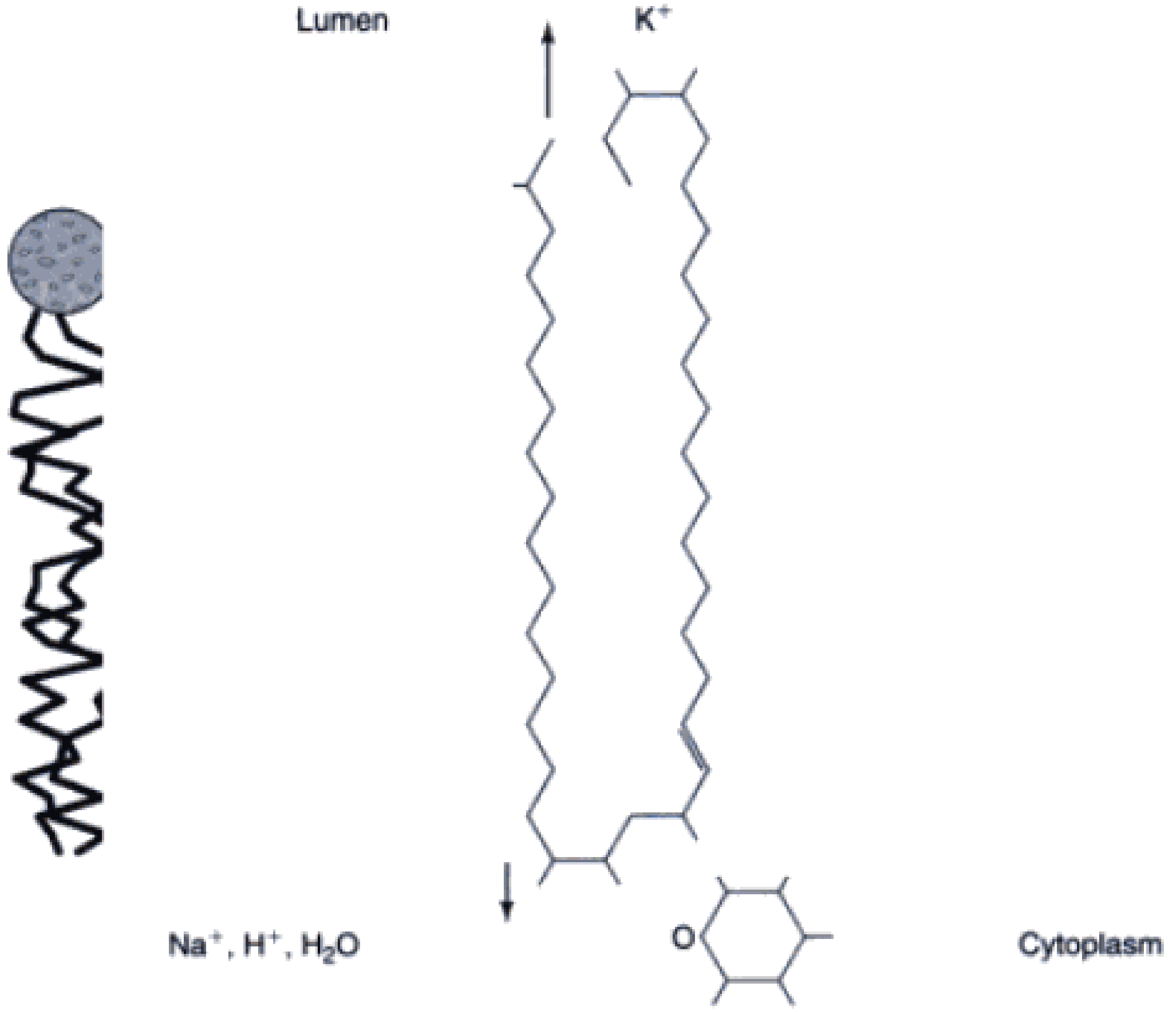

Figure 11–2. The mechanism of action and nephrotoxicity of amphotericin B reflect binding of the drug to ergosterol, the major sterol in fungal cell walls. Binding results in cell membrane permeability and the loss of critical micronutrients and electrolytes.

ment of resistance may be related to changes in the number of sterol components in the fungal cell wall. The azole derivatives may contribute to amphotericin B resistance by preventing the formation of ergosterol, the target of amphotericin B (McGinnis and Rinaldi, 1996).

Amphotericin appears to act synergistically with the following: 5-flucytosine against cryptococcosis, tetracyclines against coccidioidomycosis, and imidazoles (see later) for a variety of fungal disorders. The use of synergistic combinations may enhance efficacy while reducing the potential of toxicity.

Pharmacokinetics

Amphotericin is not water soluble and thus is not bioavailable after oral administration. It is more than 90% bound to circulating serum lipoproteins (including cholesterol). Penetration into the pleura, peritoneum, inflamed tissues, cerebrospinal fluid (CSF), and aqueous humor may result in a drug concentration two thirds of that in the plasma. The metabolism and excretion of amphotericin is not well characterized and is complex, being complicated by binding to cholesterol, which is structurally similar to ergosterol (Fig. 11–3). Biliary elimination may be the primary method of excretion (in people, only 3% of the drug is eliminated in the urine); however, concentrations are detectable in both bile and urine for up to 7 weeks in human patients.

Preparations

Because amphotericin is unstable, it is prepared as a lyophilized cake form. Deoxycholate (bile salt) is added to aid solubilization of the drug, which, when reconstituted, is in a colloidal suspension. The drug should be administered only intravenously, with exceptions for localized treatment in selected body tissues or fluids (e.g., aqueous humor, CSF). For small animals, which do not require a complete vial, the reconstituted drug can be divided into smaller aliquots and frozen. A topical preparation is also available in cream, lotion, and ointment forms.

Side Effects

Nephrotoxicity is the major toxicity associated with the use of amphotericin B. Renal function becomes impaired in more than 80% of patients receiving amphotericin (Benson and Nahata, 1988; Bennett, 1990a). Renal toxicity depends

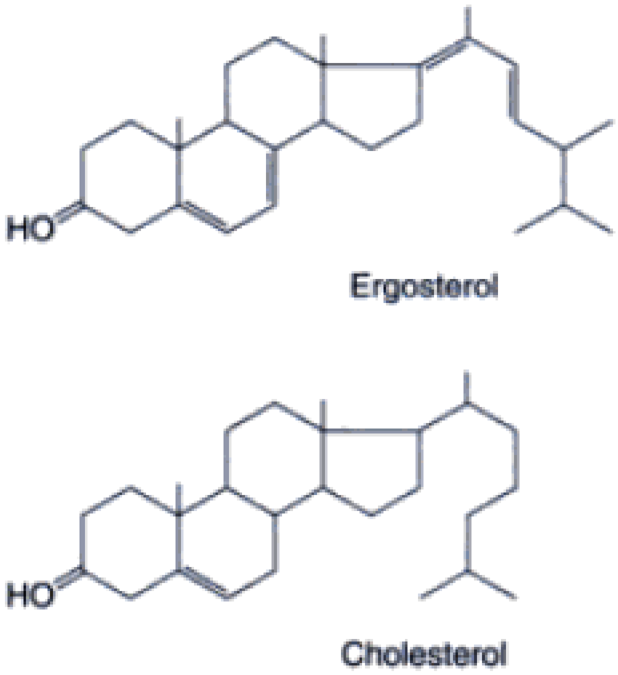

Figure 11–3. Cholesterol, the major sterol of mammalian cells, is structurally similar to ergosterol, the major sterol of fungal cell walls. Binding of amphotericin B to cholesterol results in complicated pharmacokinetics as well as host toxicity.

on total cumulative dose and duration of therapy. Although renal function usually returns to normal before completion of therapy, some residual damage often persists after discontinuation of the drug. Two mechanisms are important in renal toxicity. Intense arterial vasoconstriction occurs within 15 minutes of administration and lasts 4 to 6 hours. The mechanism is unknown but can lead to acute tubular nephrosis secondary to ischemia. Distal renal tubular toxic effects result from binding of membrane cholesterol in the tubular cell membrane (see Fig. 11–2). Altered electrolyte fluxes result in acidification abnormalities (metabolic acidosis), hypokalemia, and concentrating defects (polyuria/polydypsia).

The toxicity of amphotericin may be enhanced with catabolic drugs such as glucocorticosteroids, antineoplastic drugs, antiprostaglandins (glucocorticoids and nonsteroidal anti-inflammatory drugs), and other nephrotoxic antibiotics. Acute anaphylactic-type reactions such as vomiting, fever, and chills can occur with the use of amphotericin B. Up to 30% of dogs receiving amphotericin B develop fever (Legendre, 1984). The frequent incidence of these reactions often leads to pretreatment for anaphylaxis (one time use of a short-acting glucocorticoid does not enhance the toxicity of amphotericin B; see discussion of "cocktail" in the following section). Other side effects associated with amphotericin B include nausea and anorexia, thrombophlebitis, cardiac arrhythmias and related toxicities, hepatic dysfunction, and central nervous system signs (if given intrathecally). Several side effects can be avoided by proper treatment (see following discussion of therapeutic use).

Therapeutic Use

Amphotericin is usually administered intravenously over 4 to 6 hours in a "cocktail" designed to reduce nephrotoxicity. Doses, frequency of administration, concomitant therapy, and duration vary, with no protocol being superior to others. Some literature supports rapid intravenous (IV) administration (bolus) in less debilitated dogs; slow IV administration might be more prudent in cats. A dose (0.25 to 0.5 mg/kg) can be diluted in 300 to 1000 mL of 5% dextrose and administered in an indwelling catheter over 2 to 6 hours, or it can be diluted in as little as 10 to 60 mL and given over 2 to 5 minutes through a butterfly catheter (Greene, 1990). The slow infusion method has the added advantage of additional fluids, which may reduce the incidence of nephrotoxicity (Rubin et al., 1989), especially in debilitated animals. It is recommended that the small bolus be preceded or followed up with supplemental fluid, preferably normal saline.

The sequence of repetitive treatments is also controversial: Some authors recommend alternate-day therapy, while others recommend daily therapy at a smaller dose. Doses also vary. Daily doses range from 0.15 to 0.5 mg/kg every other day (on Monday, Wednesday, Friday) until a cumulative dose of 4 to 12 mg/kg (depending on the organism or if therapy is combined with another antifungal) has been reached. Starting at a low dose (0.15 to 0.25 mg/kg) and gradually increasing the dose until the desired daily dose has been reached may reduce the severity of side effects. For particularly resistant infections, a dose of 1 mg/kg has been used on an alternate-day basis.

Urine sediment initially should be monitored for evidence of nephrotoxicity. Serum chemistries tend to be less sensitive indicators of nephrotoxicity. The drug should be temporarily discontinued (24 to 48 hours) if the blood urea nitrogen becomes abnormal (Green, 1990). Localized mycotic infections have been treated with localized administration of amphotericin, which may reduce the incidence of nephrotoxicity: Subconjunctival, intravitreal, intrathecal, intranasal (human aspergillosis: 5 mg/ml in water administered as aerosol), and intraperitoneal routes have been reported. Oral administration has been used for treatment of gastrointestinal candidiasis and presumably might be used for other gastrointestinal fungal disorders (Stevens, 1996). One report of an uncontrolled clinical trial describes the successful and apparently safer administration of amphotericin B after two to three times weekly subcutaneous administration (0.5 to 0.8 mg/kg diluted in 400 to 500 mL of fluid such that amphotericin B is less than 20 mg/L) for several months for treatment of cryptococcosis in dogs and cats (Malik et al., 1996). However, only five successful cases were described, and further confirmation should be expected before this route is routinely embraced.

Three strategies may help reduce toxicities to amphotericin B. The first is pretreatment (to prevent vomiting, fever, chills, and anaphylaxis) with antihistamines (diphenhydramine 0.5 mg/kg, IV) and short-acting glucocorticosteroids (e.g., hydrocortisone sodium succinate, 0.5 mg/kg, IV). Because anaphylaxis appears to be associated with direct mast cell degranulation (due to the cationic nature of amphotericin B), pretreatment with a small test dose (0.1 mg/kg for cats or 0.25 mg/kg for dogs) may help detect animals that are likely to have an adverse reaction during infusion. Second, pretreatment with sodium-containing fluids is particularly important for preventing renal toxicity, including that associated with renal arterial vasoconstriction. The third strategy is administration of amphotericin diluted in 5% dextrose with mannitol (0.5 mg/kg) to maintain glomerular filtration rate and sodium bicarbonate (1 to 2 mg/kg) to prevent cellular acidification defects. The mannitol and sodium bicarbonate should not be added directly to the amphotericin B solution but given through another catheter in order to avoid precipitation of amphotericin B. The ability of "cocktails" to prevent nephrotoxicity is controversial, but most investigators agree that such cocktails are not harmful as long as the solutions are not mixed with amphotericin B. Amphotericin should not be mixed with solutions containing electrolytes, acidic solutions, or preservatives, as these materials may cause drug precipitation. The rate at which amphotericin B is administered may also reduce the incidence of nephrotoxicity.

More recent attempts to reduce the incidence of nephrotoxicity of amphotericin B have centered on specialized delivery systems (in lipids) that are designed to deliver more drug selectively to the site of infection (Leenders and de Marie, 1996). A liposomal carrier system (L-AMB) has been developed for the administration of amphotericin B and other polyene antibiotics (Juliano et al., 1992). Drug uptake by the hepatic and splenic macrophages and in inflammatory tissues is enhanced because of the phospholipid vesicle. Some studies have shown that amphotericin

B is selectively transferred from liposomes to fungal but not host cell membranes. Prolonged antifungal activity (compared with nonliposomal preparations) have been documented for these preparations. These products appear to be equal in efficacy to nonliposomal products, but safer with regard to nephrotoxicity. They tend to be very expensive. One study reports the efficacy and safety of a liposomal product when used at higher than recommended cumulative doses for treatment of canine blastomycosis (Krawiec et al., 1996).

Amphotericin B is also being prepared in various fat emulsions (cholesterol sulfate [Amphocil], lipid complexed [Abelcet]), again in an attempt to decrease nephrotoxicity. Liposomal and lipid emulsion products may be more likely than nonlipid products to cause vomiting, nausea, and phlebitis (Greene, 1998). In contrast to liposomes, fat emulsions are easy to prepare and administer and are thus more cost effective. In one study, however, although the products were equally efficacious, the degree of nephrotoxicity between a fat emulsion and standard amphotericin B was no different (Randall et al., 1996). Further studies documenting the efficacy and safety of liposomal or fat emulsion products containing amphotericin B are needed.

Finally, as previously discussed, alternative routes of administration for amphotericin B should be considered. Amphotericin B can be mixed in sterile water to 200 mg/kg and infused into the bladder for fungal cystitis. For fungal infections of the central nervous system, the drug can be given (0.2 to 0.5 mg in either 5 mL of CSF or 10% dextrose) intrathecally (under general anesthesia) two to three times per week (Greene, 1990). Combination antifungal therapy also is strongly encouraged in order to enhance efficacy and thus decrease the duration of antifungal exposure to the host.

IMIDAZOLE DERIVATIVES

Structure-Activity Relationship

The azole derivatives (imidazoles and triazoles) include a large number of predominantly synthetic drugs. These drugs consist of a five-member ring with other aromatic rings attached via a carbon nitrogen bond. Imidazoles contain two nitrogen atoms; triazoles contain three (see Fig. 11–1) (Cleary, 1992a and b; Bennett, 1990a and b; Benson and Nahata, 1988; Pasko, 1990). Examples include ketoconazole (the prototype), miconazole, clotrimazole, and thiabendazole and the newer drugs fluconazole, itraconazole, enilconazole, and terconazole. These compounds are not generally available as solutions because they tend to be insoluble in water (an exception is fluconazole). They are, however, soluble in organic solvents such as propylene glycol.

Mechanism of Action

As with amphotericin, the antifungal activity of ketoconazole derivatives is through interference with the fungal sterol ergosterol. The imidazole derivatives do not, however, bind to ergosterol but block its synthesis via inhibition of fungal cytochrome P450 enzymes. Cell membrane fluidity decreases as cell permeability increases, resulting in a fungistatic effect (fluconazole and ketoconazole). At higher concentrations, these agents also interfere with physiochemical intracellular processes of the fungal organism resulting in fungicidal effects. Because of their ability to generate and detoxify intracellular hydrogen peroxide, selected drugs also express antibacterial, antiprotozoal, and anthelmintic activities. The imidazoles are also characterized by immunomodulatory effects, which may facilitate effective therapy. Because their mechanism of action depends on cell wall synthesis, the onset of action of the imidazoles may result in a lagtime to therapeutic efficacy. In addition, a long elimination half-life of some members of this class (e.g., itraconazole) results in a lagtime as steady-state concentrations are achieved.

Spectrum of Activity

Although the imidazole derivatives are more selective in their cellular activity than amphotericin B (i.e., impairing the synthesis of rather than binding to ergosterol), their spectrum of activity is broad and includes the dermatophytes ("ringworm": *microsporum* and *trichophyton* species), yeasts, dimorphic fungi (blastomycosis, histoplasmosis, cryptococcosis, coccidioidomycosis), *Eumycetes, Actinomyces,* and some *Phycomycetes* (Grant and Clissold, 1989; Benson and Nahata, 1988; Bennett, 1990a and b; Greene, 1990; McGinnis and Rinaldi, 1996; Van Custum et al., 1987). The efficacy against these organisms varies. Studies comparing the efficacies of the azoles in animals are limited at the time of this publication, although several are pending in the human literature.

In general, itraconazole and fluconazole are more efficacious against many organisms than ketoconazole. Ketoconazole has been used effectively for dermatophyte infections, mucocutaneous candidiasis, and many systemic mycoses such as blastomycosis, histoplasmosis, and cryptococcosis in both dogs and cats. Ketoconazole should probably not be used alone for treatment of canine blastomycosis; recommendations are to use amphotericin in addition to ketoconazole. Ketoconazole has little efficacy (43%) against *Aspergillosis* species. Fluconazole (60% efficacy) appears to be less active than itraconazole (60% to 70% efficacy) against this organism. For itraconazole, efficacy against *Aspergillosis* is better than that clinically recognized for any other agent, although treatment failure rates of up to 50% have been reported for itraconazole. In animals, administration of itraconazole at a rate of 5 mg/kg twice daily is efficacious in the treatment of blastomycosis and histoplasmosis. The efficacy of itraconazole against coccidioidomycosis is equivocable, requiring long-term therapy. Relapse of disease appears to be common.

In vitro MIC data regarding the relative susceptibility of selected organisms to itraconazole emphasize the variable susceptibility of fungal organisms to these drugs. For itraconazole, the reported MIC_{90} concentrations include 0.130 µg/mL for *Blastomyces* species and *Aspergillus fumigatus,* 0.63 µg/mL for *Cryptococcus neoformans* and *Histoplasma capsulatum,* and 0.4 µg/mL for *Sporothrix schenckii.* For dermatophytes, the MIC_{90} concentration for *Microsporum* species is 250 μg/mL and for *Trichophyton* species, 4.0 μg/mL. Despite the larger MIC for dermatophytes, however, itraconazole at 1.5 to 3.0 mg/kg every 24 hours was effective in 8 of 15 cats in one uncontrolled clinical trial for treatment of dermatophytosis (Manciati et al., 1998). For other *Eumyctes*, MIC$_{90}$ concentrations range from 0.130 μg/mL to more than 128 μg/mL (Borgers, 1987; Grant and Clissold, 1989).

Fluconazole has been used successfully to treat ketoconazole-resistant strains of *Candida*. Equal efficacies of itraconazole and fluconazole have been shown for cryptococcal meningitis, despite relatively poor penetration of the CSF by itraconazole. Both are equally effective in *candida*-induced pyelonephritis. Newer azoles are likely to prove yet even more efficacious than fluconazole and itraconazole for the treatment of aspergillosis and coccidioidomycosis. Comparison between ketoconazole and fluconazole reveals fluconazole to be more active against coccidioidal meningitis.

Some gram-positive bacteria (e.g., *Staphylococcus* species) and anaerobes are also susceptible to these imidazoles. Cutaneous infections by *Leishmania* species are clinically susceptible to ketoconazole (Hart et al., 1989). Ketoconazole and, presumably, other azole antifungals have synergistic antifungal activities with 5-flucytosine against *Candida* and *Cryptococcus* and with amphotericin against a variety of organisms.

Clotrimazole and miconazole are common drugs used topically for treatment of dermatophytosis (e.g., Conofite) or yeast (e.g., otic preparations such as Otomax). Thiabendazole is an azole antifungal that has been used (10 to 20 mg/kg orally every 12 hours) for aspergillosis (nasal, topically, and orally) and penicilliosis (efficacy 43%). For these infections it has largely been replaced by the newer azoles, although it continues to be the antifungal component of some combination topical products, targeting principally yeast (e.g., Tresaderm).

Pharmacokinetics

Oral absorption of the imidazole derivatives varies with the drug and among animals. For many drugs, oral preparations are not available. For example, enilconazole (imazalil) is not orally bioavailable. For other imidazoles, the rate of absorption varies from 1 to 4 hours. Oral absorption often depends on gastric pH, product preparation, and the presence of other drugs (Hardin, 1988). Absorption of itraconazole and ketoconazole is enhanced by gastric acidity; these drugs should be administered with food (Van Peer et al., 1989). Alkalinizing drugs administered orally will decrease their absorption. Peak plasma drug concentrations of itraconazole occur between 1 to 5 hours in cats and dogs. Bioavailability of capsules is approximately 20% in dogs and may be as little as 10% in cats compared with close to 50% for the solution in cats and dogs (Boothe et al., 1997; Heykants et al., 1987). Decreased bioavailability may be responsible for therapeutic failure associated with low plasma drug concentrations in some animals (cats and dogs). Fluconazole is characterized by the best oral bioavailability among the imidazoles, being completely absorbed in cats (Vaden et al., 1997).

Distribution to tissues also varies among the imidazoles. Ketoconazole is up to 99% protein bound; the highest tissue levels occur in the liver, lung, and kidney (and cerumen). Itraconazole is also very highly protein bound in humans (Bennett, 1990a). There is minimal penetration of the CSF by ketoconazole, although fluconazole penetrates the CSF well, with serum to CSF plasma drug concentrations ranging from 0.58 to 0.89 μg/mL. The volume of distribution of ketoconazole is only 0.87 L/kg in dogs compared with 17 L/kg for itraconazole in dogs (Heykants et al., 1987) and 5 L/kg in cats (Boothe et al., 1997). The volume of distribution of fluconazole is 1.14 L/kg in cats, with high concentrations occurring in the CSF and aqueous humor (Vaden et al., 1997). The difference in distribution volume reflects, in part, distribution and accumulation to fat (Hrykants et al., 1987). Drug concentrations of itraconazole in the skin may exceed that in plasma by 3-fold to 10-fold, with drug detectable 2 to 4 weeks after therapy is discontinued (Heykants et al., 1987). Although distribution of itraconazole to the CSF appears to be limited, therapeutic concentrations appear to be achieved in patients suffering from cryptococcal meningitis. Among the azole derivatives, fluconazole has the best tissue distribution pattern and can achieve effective concentrations in CSF.

With the exception of fluconazole, the azole derivatives are eliminated by extensive oxidative (cytochrome P450) metabolism with excretion as inactive metabolites into the bile and urine. Metabolism may be dose dependent; elimination rate constants are lower and half-lives are longer at higher doses and with longer therapy. In contrast to the other imidazoles, fluconazole is eliminated principally (70%) in the urine. The half-life of the imidazoles varies, with that of ketoconazole being relatively short (1.4 hours in dogs). Fluconazole and itraconazole have longer half-lives, ranging from 22 to 32 hours in people, 51 hours in dogs (itraconazole), and 25 hours in cats (fluconazole) (Vaden et al., 1997) and 40 to 70 hours in cats (itraconazole) (Boothe et al., 1997). The longer drug elimination half-life must be taken into account because it results in a longer time to steady-state concentration and maximum therapeutic effect.

Preparations

Ketoconazole, itraconazole, and fluconazole are available for oral administration. Solutions are available for some products (e.g., ketoconazole), but their safety has not been documented for animals. The solubility of imidazoles is poor and potentially toxic; solubilizing agents may be the cause of adverse reactions. Cats appear to tolerate a single 5 mg/kg dose of itraconazole IV with no adverse affects, although this product is not commercially available. Clotrimazole and miconazole are recommended only for localized dermatophyte or yeast infections susceptible to topical treatment. Clotrimazole has been used topically to treat nasal aspergillosis. Thiabendazole is available as a topical preparation (and as a drench intended for anthelmintic therapy). Enilconazole is a topically effective azole that has been used to treat nasal aspergillosis but is available in the United States only as a 13.8% poultry dip. It is available in Canada as a 10% solution approved for use in dogs and horses. The poultry dip has been used topically in the United States at a dilution of 1:50 in water in dogs and cats with no apparent adverse effects. Terconazole is a new, topically active triazole that apparently has not yet been used for animals.

Drug Interactions and Side Effects

Because the azoles interfere with synthesis of ergosterol rather than binding the sterol, the host toxicities typical of those induced by amphotericin do not occur (Van Cauteren, 1987). Gastrointestinal toxicities are the most common and are not severe (Benson and Nahata, 1988; Bennett, 1990a and b; Greene, 1990; Legendre et al., 1996; Manciati et al., 1998). Nausea and vomiting can usually be avoided by administration of the drug with food. Hepatotoxicity with ketoconazole has been reported in humans. Isolated cases of hepatotoxicity have been reported with itraconazole and fluconazole. A dose dependency has been documented in one case with fluconazole. Patients with impaired liver function may be predisposed to worsening hepatic function induced by the azole antifungal drugs. The occurrence of liver disease in animals treated with itraconazole is controversial. Cats receiving 5 and 10 mg/kg twice daily showed no adverse effects (including weight loss) after receiving itraconazole for 6 weeks (Boothe et al., 1997). One case of cutaneous drug eruption typical of erythema multiforme caused by itraconazole has been reported in a dog (Plotnick et al., 1997); idiopathic vasculatis has also been reported (Legendre et al., 1996). Nausea, vomiting, skin rash, thrombocytopenia, and hypokalemia have also been reported with fluconazole therapy.

Because the efficacy of the azoles depends on interaction with cytochrome P450 (an oxidative enzyme responsible for drug metabolism), drug interactions at the level of metabolism should be anticipated. Ketoconazole inhibits microsomal enzymes, whereas clotrimazole is a potent inducer. The use of ketoconazole therapeutically to inhibit the metabolism of cyclosporine—thus allowing a dose reduction of cyclosporine—is addressed in Chapter 19. Ketoconazole interferes with sex hormones and corticosteroids by displacing them from globulins and perhaps by interfering with their synthesis. As a result of its effects on steroid synthesis, ketoconazole has been used to treat hyperadrenocorticism and to impair testosterone synthesis in patients with prostatic hypertrophy or prostatic cancer. Ketoconazole has caused lightening of the haircoat of some dogs (Willard, 1986a). Willard reported depressed basal cortisol and testosterone concentrations and ACTH response by cortisol at 30 mg/kg/day. A rebound response was seen after ketoconazole was discontinued. Serum progesterone concentrations were also decreased. Aldosterone was not decreased. Cats receiving 30 mg/kg/day for 30 days developed dry hair coat and weight loss but no changes in testosterone or progesterone concentrations (Willard, 1986b). Itraconazole also inhibits cytochrome P450 enzymes (Bosscher, 1987; De Coster, 1987). Although itraconazole clinically is not generally recognized to inhibit drug metabolism, changes in the elimination half-life have been documented in cats receiving long-term therapy (>6 weeks).

Therapeutic Use

Among the imidazoles, itraconazole and fluconazole are being used more consistently than the others for systemic treatment of susceptible fungal infections. The efficacies of selected fungal agents are discussed later. Ketaconazole has been reported to be effective treatment of dermatophytosis (Medleau and Chalmers, 1992; Mundell, 1990), blastomycosis (Dunbar et al., 1983), histoplasmosis (Noxon et al., 1982), coccidioidomycosis (Malik et al., 1992), and cryptococcosis (Noxon et al., 1986). For itraconazole (Tucker, 1988), conditions successfully treated include blastomycosis (Legendre et al., 1996) (including ocular [Brooks 1991]), histoplasmosis (Hodges et al., 1994), cryptococcosis (including meningitis) (Medleau 1990; Medleau et al., 1995), sporotrichosis (Peaston, 1993), aspergillosis (Legendre, 1995), dermatophytosis (Manciati et al., 1998), dermatophytic pseudomycetomas (DeBoer et al., 1995; Medleau and Rakich, 1994), phaeohyphomycosis (Michaud, 1993), and cutaneous *Alternaria* (Simons 1993).

The dermatologic pharmacokinetics of itraconazole support pulse therapy, which has been used in human medicine for treatment of selective dermatologic fungal disorders. Treatment occurs for two consecutive weeks of daily administration each month for three consecutive months (Guptal et al., 1997). One report of itraconazole used to treat dermatophytosis reports similar success with this technique (Manciati et al., 1998). There are few reports regarding the efficacy of fluconazole for treatment of fungal infections in animals; infections that have been treated include blastomycosis (Hill et al., 1995), cryoptococcosis (Malik et al., 1992), and nasal aspergillosis (Sharp et al., 1991). Efficacy has, however, been demonstrated toward a variety of fungal disorders in humans. Pulse dosing (once weekly) of fluconazole also has been described for treatment of skin infections in people. Enilconazole has excellent in vitro activity against a number of organisms, but its topical use is limited to dermatophytes and nasal aspergillosis.

FLUCYTOSINE

Structure-Activity Relationship

5-Flucytosine (FLU; 5-fluorocytosine) was originally developed as an anticancer drug much the same as its sister anticancer drug, 5-fluorouracil. It is a water-soluble powder.

Mechanism of Action

As an antimetabolite, FLU interferes with DNA synthesis after its conversion to 5-fluorouracil, a substitution compound that prevents synthesis in the fungal cell (Benson and Nahata, 1988; Bennett, 1990a and b). The enzyme responsible for conversion to 5-fluorouracil, a cytosine deaminase, is not present in mammalian cells. Fluorouracil undergoes additional metabolism before its inhibition of thymidylate synthase and DNA synthesis. Flucytosine is fungistatic and has no antibacterial activity. Many organisms are resistant to FLU because they lack the permease enzyme or other enzymes responsible for FLU activity. Resistance develops relatively rapidly, particularly for cryptococcosis and candidiasis. Use in combination with another antifungal agent reduces the development of resistance.

Spectrum of Activity

The spectrum of activity of FLU is limited and includes cryptococcosis, candidiasis and some cladosporiosis, aspergillosis, chromomycosis, and sporotrichosis. It has been the treatment of choice for cryptococcosis in humans (Benson and Nahata, 1988; Bennett, 1990a and b). Combination therapy is usually indicated (e.g., amphotericin, ketoconazole). When FLU is used alone, resistance develops rapidly. Synergism occurs with amphotericin B and probably with ketoconazole (or other imidazoles).

Pharmacokinetics

Oral absorption of FLU is rapid and close to complete. Peak plasma concentrations occur in 1 to 2 hours. Distribution is large, to total body water. Protein binding is minimal, and CSF concentrations reach up to 90% of plasma concentrations. Penetration of aqueous humor and joints is good. The half-life of FLU is 3 to 6 hours. Most of the drug is excreted into the urine unchanged. Renal clearance is similar to that of creatinine and thus may be significantly slowed if renal dysfunction is present. Doses will probably need to be modified for patients with renal disease.

Preparations

Flucytosine is available as an oral preparation.

Side Effects

Because FLU interferes with DNA synthesis, body systems composed of rapidly dividing cells are adversely affected. Bone marrow depression is manifested as anemia, leukopenia, and thrombocytopenia (pancytopenia). This toxicity may be serious and is more common in patients with renal disease. Gastrointestinal toxicity is manifested as nausea, vomiting, and diarrhea, but it is not usually serious. Reversible, erythremic, alopecic dermatitis has been reported in the dogs.

GRISEOFULVIN

Structure-Activity Relationship

Griseofulvin (see Fig. 11–1) is produced from a *Penicillium* species bacterium. The drug is insoluble in water.

Mechanism of Action

Griseofulvin enters fungi through an energy-dependent transport system. Griseofulvin inhibits fungal mitosis by binding to the microtubules that form the mitotic spindle. The formation of microtubules from tubulin is inhibited. Other drugs, such as colchicine and vincristine, which also bind to and inhibit the microtubule, do so at a site that is different from that of griseofulvin. Griseofulvin also probably inhibits nucleic acid and fungal wall synthesis. It is not certain if griseofulvin is fungistatic or fungicidal. Resistance probably reflects decreased drug uptake.

Spectrum of Activity

The spectrum of activity is limited to dermatophytes: *microsporum, trichophyton,* and *Epidermophyton.* Because of its distribution into keratin, griseofulvin remains the drug of choice for fungal infections of the nails.

Pharmacokinetics

Griseofulvin is insoluble. Oral absorption varies due to this insolubility and depends on particle size and preparation. Absorption is increased in the presence of fat. The rates of dissolution and disaggregation alter the bioavailability of different products. Bioavailability of the ultramicrosize is at least 50% greater than that of the microsize. Although griseofulvin penetrates the stratum corneum, it does not achieve effective concentrations topically. Griseofulvin is widely distributed to most tissues, but it is deposited and concentrated in keratin precursor cells. Thus, it is incorporated in new keratin of skin, nails, and hair and (in humans) is secreted in perspiration. Although new keratin formed during treatment with griseofulvin is resistant to fungus, griseofulvin does not destroy fungi that infect the outer layers of the skin. New hair, skin, or nail growth accompanied by shedding of older growth is necessary before the fungus is affected; new growth is the first to be free of disease. Thus, skin infections require 4 to 6 weeks of therapy, whereas toenails may require up to a year of therapy.

Hepatic metabolism of griseofulvin by dealkylation is significant; metabolites are not active. The half-life reportedly is 24 hours in the dog. Half of the drug is excreted as metabolites in the urine. The rest is excreted unchanged in the feces.

Preparations

Griseofulvin is available for oral use as either a microsize (particle size 10 μm) or ultramicrosize (particle size 2.7 μm; e.g., Fulvicin, Gris-Peg) tablets. The drug should be administered with a fatty meal, particularly if the microsize preparation is used. Duration of therapy is *at least* 4 to 6 weeks (new hair growth must occur) and possibly longer. The drug should be administered at least once a day despite initial reports that recommend one weekly administration.

Side Effects and Drug Interactions

Side effects are not uncommon. Nausea, vomiting, and diarrhea can be minimized by administration of the dose in divided increments with a meal. Hepatotoxicity may occur, and use in liver disease should be avoided. Idiosyncratic toxicity has been recently reported in the cat manifested as gastrointestinal upset, neurologic disease, and bone marrow suppression (Helton et al., 1986). The reaction appears to be both dose and duration independent. Signs may or may not be reversible, depending on the severity. Cats with feline immunodeficiency disorders may be more likely to develop neutropenia (Sheltin et al., 1990): feline breeds (Persians, Siamese, Abyssinians) may be more commonly affected (Helton et al., 1986). At very high doses, the drug is teratogenic and carcinogenic in animals. The drug should not be given during the first two trimesters of pregnancy.

Griseofulvin is a potent inducer of microsomal enzymes. The clinical sequelae of this drug interaction are not well known, although increased metabolism of other drugs should be anticipated.

ALLYLAMINES

The mechanism of action of the allylamines, a recently introduced group of antifungals, is similar to that of the tolycyclate antifungals (e.g., tolnaftate) in that squalene, important in the formation of the cell membrane (before the formation of ergosterol), is inhibited. Naftifine and terbinafine are the two major drugs in this group. They act to inhibit squalene epoxidase, blocking conversion of squalene to lanosterol, which depletes ergosterol. Because of avid uptake of terbinafine into body fat and epidermis, its efficacy appears to be limited to dermatophytes and superficial pathogens of the skin. Efficacy has also been demonstrated against *Sporothrix schenckii* and *Aspergillus* species. Antifungal effects are cidal in these organisms. Fungistatic efficacy has been demonstrated against yeasts (Balfour et al., 1992). It has, however, proven more efficacious than griseofulvin for both acute and chronic dermatophyte infections in people. Current efforts are oriented toward applying this drug to the treatment of systemic fungal infections.

Terbinafine is well absorbed after oral administration, although fat facilitates absorption. High concentrations occur in the stratum corneum, sebum, and hair. The drug is metabolized by the liver in humans; the elimination half-life is sufficiently long to allow once-daily dosing (Feargemann et al., 1990). Use of terbinafine in animals has not been reported in the United States, although an abstract reporting pharmacokinetics in cats suggested that a dose of 20 to 40 mg/kg once daily provided sufficient concentration of drug in the skin. The drug was well tolerated at this dose (Sparks, 1996). Because inhibition of ergosterol synthesis does not involve cytochrome P450, the allylamines do not affect steroid synthesis as do the imidazoles.

IODIDES

The mechanism of antifungal action of the iodides is not known. Iodide is rapidly and completely absorbed orally. Distribution is to the extracellular fluid. Thyroid uptake will concentrate the drug up to 50 times that in plasma. Iodide is available as a 20% Na and K^+ salt oral or intravenous preparation. Both salts have been used successfully to treat canine and feline cutaneous or lymphocutaneous forms of sporotrichosis, and, as such, it remains the drug of choice (Werner and Werner, 1993; Moriello et al., 1988). Oral Na^+ preparations are usually used. Iodide toxicity is more common in cats and is manifested as sweating, tachycardia, dry scaly coat, diarrhea, and polyuria/polydypsia. Cardiomyopathy has been reported in cats. Treatment causing clinical signs of iodinism should be discontinued for 1 week and then reinstituted at a lower dose. Iodine has also been reported to be effective for various other fungal diseases, particularly as a topical ointment for localized skin infections.

THERAPEUTIC USE OF ANTIFUNGAL AGENTS

Topical Fungal Infections: Dermatophytosis

A number of fungal organisms inhabit the haircoats of dogs and cats. *Alternaria, Cladosporium,* and yeasts may be associated with dermatitis. Dermatophytes can be isolated from normal animals or can be a cause of infection. Dermatophyte infections generally are self-limiting, with the ability to mount an inflammatory response being important to control of infection. Hence, drugs such as glucocorticoids, which prevent an inflammatory response in the skin, predispose a patient to dermatophyte infection. The route of drug administration (topical vs. systemic therapy) depends on the extent of infection, with the exception of *Trichophyton* infections, which should be treated systemically.

Topical therapy is indicated for all patients with dermatophytosis and may be the sole therapy for local, nondiffuse lesions. Haircoat preparation before medication should include clipping and bathing to remove hair and crusts. Several medicaments are available as shampoo, ointment, or cream for topical therapy (Table 11–2). Active ingredients include povidone-iodine, chlorhexidine, and imidazole. Other active ingredients that can be applied topically include captan, lime sulfur, and sodium hypochlorite. Short-term topical glucocorticoid therapy might be considered to control acute inflammation when present. Topical administration of enilconazole emulsion has been useful for treatment of feline dermatophytosis.

Systemic therapy should probably be preceded with a total body clip. Griseofulvin is the treatment of choice for long-term systemic antifungal therapy of dermatophytosis (Foil, 1990), although expense mandates that a diagnosis of dermatophytosis be confirmed. Care should be taken that the proper dose and duration of therapy are followed. For infections that do not respond to griseofulvin, an imidazole can be used. Ketoconazole has been used successfully, particularly when dosed at 10 mg/kg daily for 20 days. Itraconazole has, however, proved more efficacious for treatment of dermatophytes in human patients and has proved efficacious experimentally in cats infected with *Microsporum canis* (Moriello and DeBoer, 1995) at 10 mg/kg orally once daily. Manciati et al. (1998) report pulse

Table 11–2. Dosing Regimens for Antifungal Drugs*

Drug	Route	Dose (mg/kg)	Frequency
Systemic			
Amphotericin B†	IV	D: 0.25–0.5	3×/week or 48 h
		C: 0.1–0.5	3×/week or 48 h
		(0.4–0.5)‡	3×/week or 48 h
	SC	0.5–0.8 mg/kg	3×/week or 48 h
	Aerosol	5 mg/mL (5% dextrose)	
L-AMB (AmBisome)	IV	1–3.3‡	48–96‡
Amphocil	IV	1–2.5	3×/week or 48 h
Abelcet	IV	1–2.5	3×/week or 48 h
Enilconazole	Topical	10 q12h§	3×/week or 48 h
Flucytosine‖	PO	D & C: 2.5–5	12–24 h
		C: 30–75‖	6–8h
		50‖	12
Fluconazole	IV (D), PO	5–10	q12–24h
		2.5–5.0	q12–24h
Griseofulvin	PO	25–60 (microsized [maximum 110–132 mg/kg])	q24h
		2.5–15 (ultramicrosized)	q12–24h**
Iodine	PO	D: 10–40	8–12 h
		C: 10–20	12–24 h
Itraconazole††	PO	5–10	12–24 h
		20	24h
Ketoconazole‡‡	PO	D: 5–20	8–12h
		C: 5–10 or 10–20§§	12 or 24 h
		30	24h
Dapsone		1	12 h‖‖
Rinses			
Captan		2% (2 tbs/gallon water)	Rinse
Chlorhexidine		0.5%–2% rinse	Daily
		Shampoo	Every 5 days
Lime sulfur		2% rinse	Every 5–7 days
Povidone-iodine		1 : 4 in water	Daily
Sodium hypochlorite (bleach)		1 : 20 (0.5%) in water	Every 5–7 days
Ointments or Creams			
Clotrimazole			Twice daily
Ketoconazole			Twice daily
Miconazole			Twice daily

Abbreviations: 3× = three times; C = cat; D = dog; IV = intravenous; PO = oral; SC = subcutaneous.

*Minimum duration of treatment is 4 to 6 months; cryptococcosis may be 1 to 9 months; coccidioidomycosis, 6 to 12 months. Doses are from Greene's *Infectious Diseases of the Dog and Cat* (1990).

†Total cumulative dose of 4–10 mg/kg in dogs (8–11 mg/kg if coccidioidomycosis) or 4–8 mg/kg in cats. Follow with ketoconazole for blastomycosis and use in combination with flucytosine for cryptococcosis and tetracycline (22 mg/kg q8h) for protothecosis.

‡Higher dose used for blastomycosis and coccidioidomycosis. Use at 30-day intervals for prevention of relapse. *For L-AMB, leishmaniasis will require a higher dose at 72- to 96-hour intervals for a cumulative dose of 15 mg/kg; other mycoses, 1–2.5 mg/kg at 48-hour intervals for a cumulative dose of 12 mg/kg. For more resistant infections 2–2.5 mg/kg is administered to a cumulative dose of 24–30 mg/kg (Greene, 1998).*

§Nasal aspergillosis. Duration 1 week (80%–90% efficacy).

‖Use in combination with amphotericin B for cryptococcosis; reduce dose to 50 mg/cat if toxicity occurs. Higher doses reflect clinical reports for treatment of cryptococcosis in cats.

¶Histoplasmosis.

**Duration for dermatophytosis, 4–6 weeks.

††Investigational new drug.

‡‡Add amphotericin B if coccidioidomycosis titers rise or do not respond after 3–4 weeks of therapy. Maintenance dose (prevent relapse) for coccidioidomycosis: 2–5 mg/kg q24h. Duration, 3–4 weeks for dermatophytosis.

§§A dose as high as 70 mg/kg/day may be necessary if tolerated.

‖‖For treatment of *Rhinosporidium;* treat for 4 months.

therapy with itraconazole (15 days of oral therapy followed by 15 days of no treatment for two to three cycles as needed) effective for treating dermatophytosis in cats.

Cleansing of the environment can be accomplished with either 2% chlorhexidine or 0.5% sodium hypochlorite.

Yeast or Yeast-Like Infections

Malassezia

Malassezia (Pityrosporum) is a commensal organism that inhabits the skin, ear canal, anal sacs, vagina, and rectum of dogs. It is now recognized to be the causative agent of either localized or generalized pruritic inflammatory skin disease in dogs. The pathogenesis of the infection is controversial and appears to involve hypersensitivity to the organism. Postulated predisposing factors include allergic disease such as atopic dermatitis, diseases of cornification, chronic inflammatory skin disease, and previous therapy with antibiotics or glucocorticoids.

Therapy for *Malassezia* is directed toward removing predisposing factors and killing the causative agent (Ihrke, 1996). Antimicrobial therapy ideally should include both systemic and topical drugs. Ketoconazole and itraconazole are the systemic drugs of choice and should be given for at least 30 days. Topical therapy may be sufficient in some cases. Antifungal shampoos containing chlorhexidine, miconazole, or ketoconazole should be given at least twice weekly for a minimum of 6 weeks. Shampoos that resolve any exudate (such as benzoyl peroxide) may facilitate topical penetration of the antifungal drug. An acetic acid rinse (white vinegar and water at a ratio of 1:1) used twice weekly as a degreasing agent after shampooing may also prove beneficial as well as inexpensive. Application of eniloconazole emulsion may also be beneficial. The emulsion can be applied with a sponge or by whole-body emersion; the diluted product appears to remain stable for 4 to 6 weeks when protected against light, although use of a fresh dilution is recommended for each treatment.

Candidiasis

In the yeast phase, candidiasis normally occurs in the gastrointestinal, respiratory, or urogenital mucosa. The organism is acquired at birth and occurs at mucocutaneous junctions in the skin and in several organs inside the body. Factors that alter normal microflora (e.g., prolonged, high-dose, broad-spectrum antimicrobial therapy) predispose the development of candidiasis. Cell-mediated immunity is important to the control of disease, and prolonged immunosuppression increases the risk of further spread. Generally, microcirculation of the organs filters organisms, leading to embolization.

Topical infection can be treated with topical antifungal products, including polyene macrolides, imidazoles, and gentian violet (1:10,000). Systemic therapy can be treated with amphotericin B, 5-flucytosine (combined with another antifungal drug), or the imidazoles.

Systemic Fungal Diseases

Therapeutic success with antifungal drugs can be enhanced by long-term therapy, generally one to several months beyond the resolution of clinical signs, avoidance of immunosuppressive drugs, and use of combination therapy, particularly for infections that are difficult to penetrate or are life or organ threatening.

Blastomycosis

Blastomyces organisms become established in the lungs and then disseminate throughout the body. The presence of clinical signs in dogs is indicative of disseminated disease and the need for aggressive therapy. Preferred sites of infection in dogs are the skin, eyes, bones, lymph nodes, subcutaneous tissues, nasal passages, and brain. These tissues are difficult to penetrate with most antifungal drugs, thus increasing the likelihood of therapeutic failure. Immunosuppression is common in dogs with blastomycosis, further hindering therapeutic success.

Amphotericin B has been the treatment of choice for blastomycosis (Legendre, 1990). Although high doses are more effective, the risk of nephrotoxicity may necessitate a less aggressive approach. Renal-sparing measures should be taken for patients with preexisting renal disease. Despite aggressive therapy, a relapse rate of 17% has been reported in dogs (Legendre, 1984). Combination therapy of amphotericin B with an imidazole should be considered whenever possible and is particularly important for infections in tissues that are difficult to penetrate such as the brain and eye. Of the imidazoles, ketoconazole has been used alone to treat blastomycosis in people, but it is less successful for animals as a sole agent. Because imidazoles are characterized by variation in drug disposition among animals, efficacy might be enhanced by increasing the dose. Although sequential use of amphotericin B followed by ketoconazole has been recommended, the two can be used in combination immediately with little to no increased risk of toxicity. The rapid effects of amphotericin B are critical for life-threatening or organ-threatening infections. Itraconazole or fluconazole are more likely to be effective than ketoconazole for the treatment of blastomycosis. Although itraconazole is more likely to be effective as sole therapy, combination therapy with amphotericin B is still recommended.

With proper therapy, up to 80% of dogs with blastomycosis can be effectively treated. The severity of pulmonary involvement appears to be a prognostic factor for both initial survival and the likelihood of relapse. Therapy may result in an initial worsening of respiratory disease, presumably due to an inflammatory response to dying organisms. Of the remaining 20% of animals, some may die within the first 2 weeks of therapy. Relapse can occur in up to 20% of infected animals within the first 6 months after therapy, but relapse after 1 year is rare.

Histoplasmosis

Host macrophages phagocytize the yeast phase of *Histoplasma,* and the organism then undergoes replication. The intracellular location is a mitigating factor in the hematogenous and lymphatic dissemination of the organisms from the lungs to other tissues. In most patients, cell-mediated immunity brings the infection under control. The gastrointestinal tract may also be a primary site of infection, although dissemination from the lungs appears to be more likely (Wolf, 1990). Although pulmonary infection may be self-limiting, therapy is indicated to prevent dissemination of infection.

Ketoconazole has been the drug of choice for mild pulmonary histoplasmosis (Wolf, 1990). One study, however, reported that only itraconazole (5 mg/kg orally twice daily for 60 to 130 days) was effective against histoplasmosis in cats (Hodges et al., 1994). For more severe pulmonary infection, or gastrointestinal infection, therapy should be more aggressive. Alternatives include combination of ketoconazole with amphotericin B or sole therapy with itraconazole or fluconazole. Both of the latter drugs are much more effective (up to 100-fold) than ketoconazole against histoplasmosis. The prognosis for patients with pulmonary histoplasmosis is fair to good but guarded when the disease has disseminated.

Cryptococcosis

Cryptococcus organisms infect the upper respiratory tract or the alveoli, potentially causing granulomas at both sites.

Once established in the respiratory system, they can disseminate to other tissues. Infection of the central nervous system by either dissemination or direct extension is common. Cutaneous and ocular lesions are common in cats.

Cell-mediated immunity is critical to the host's ability to overcome a cryptococcal infection. Cryptococcal organisms have several features that impact their virulence. The capsule inhibits plasma cell function, phagocytosis, and leukocyte activity. Fever is uncommon (25% of dogs), particularly in cats. Immunosuppression is essentially necessary for cryptococcosis to develop in people. Underlying diseases are, however, not often identified in cats or dogs with cryptococcosis, although feline leukemia virus and feline immunodeficiency virus are known predisposing factors in cats.

Amphotericin B is the treatment of choice for cryptococcosis (Medleau, 1990, 1994). Initial therapy with a low dose and a subsequent increase in dose has been suggested for cats. Combination with 5-flucytosine or the imidazoles is likely to improve therapeutic success and is indicated for central nervous system infections because amphotericin B cannot sufficiently penetrate the blood-brain barrier. Ketoconazole has been used successfully to treat cryptococcosis. Itraconazole (10 mg/kg orally once daily), however, and fluconazole are more effective than ketoconazole against cryptococcosis. Cats appear to tolerate itraconazole better than ketoconazole (Medleau, 1990). Both drugs, but fluconazole even more so, are characterized by better tissue penetrability and can be used to treat central nervous system infection. One study with cats reported that 16 of 28 were cured of cryptococcosis after treatment with itraconazole (100 mg orally once daily) for a mean of 4 to 16 months (Medleau et al., 1995).

Coccidioidomycosis

Coccidioidomycosis begins as an alveolar infection that spreads to peribronchiolar tissues and the lung surface. Cell-mediated immunity is important to overcoming the infection. In immunodepressed animals, or in animals with massive exposure, pulmonary infection becomes extensive, and the infection disseminates first to mediastinal and tracheobronchial lymph nodes and then to other tissues. Organs that are subsequently infected include, in order of likelihood, bone, joints, visceral organs, the heart and pericardium, testicles, eyes, and brain.

Antifungal therapy for coccidioidomycosis is particularly long (Barsanti, 1990). The duration varies with both the site of infection and the drug and can be for the life of the animal in some cases of disseminated disease. Ketoconazole has been the drug of choice for treatment in the past, although itraconazole is more effective. Ketoconazole therapy should extend at least 1 year beyond resolution of clinical signs. Amphotericin B is also effective for the treatment of coccidioidomycosis. A lower maintenance dose of either ketoconazole or amphotericin B has been recommended once clinical signs are in remission. Deterioration of clinical signs and a rising complement fixation test are both indications for combination therapy with amphotericin B. Therapy with itraconazole may occur for a shorter time, although this has not been well established in animals. Fluconazole is indicated for central nervous system infections. Combination therapy (i.e., amphotericin B with an imidazole) should be strongly considered for treatment of coccidioidomycosis.

Aspergillosis

Aspergillosis can occur as either the localized form, involving cavities of the ears, nose, or sinuses; or the disseminated form, occuring primarily in the lung of immunocompromised animals. Both systemic and topical therapy should be implemented with either form of the disease. Systemic therapy should consist of an imidazole; among the drugs, itraconazole is the most efficacious against aspergillosis. Topical therapy has included amphotericin B, thiabendazole, and enilconazole, a topical imidazole available in Europe but not the United States. Enilconazole might be the most effective treatment when directly infused into the nasal passages through fenestrated tubes (Sharp, 1989). The 10% solution is diluted 1:1 with water and administered through surgically placed nasal tubes within 2 to 3 minutes. The solution emulsifies within several minutes of mixing; nasal tubes must be flushed after treatment. The total daily dose of 20 mg/kg is administered in two divided doses daily. Topical clotrimazole might be considered in lieu of enilconazole.

Subcutaneous Mycoses

Sporotrichosis

Sporotrichosis occurs in three clinical forms: cutaneous, cutaneolymphatic, and disseminated. Disseminated disease generally involves most internal organs. The treatment of choice for both dogs and cats is supersaturated potassium iodide (SSKI) (Rosser, 1990). Cats are more sensitive than dogs to the side effects of SSKI. Treatment should continue for at least 30 days beyond clinical remission. Immunosuppressive drugs should be avoided if possible for the duration of the animal's life; recurrence in clinically cured animals has been reported after immunosuppressive doses of glucocorticoids. Imidazoles should be used to treat animals that cannot tolerate or do not respond to SSKI. Other antifungals (e.g., terbinafine) might be combined with iodine.

Rhinosporidiosis

Rhinosporidium rarely causes disseminated disease in animals and is essentially limited to the nasal tissues. Surgical excision is the treatment of choice (Breitschwerdt, 1990). For recurrences, dapsone may be useful. Alternatively, ketoconazole or itraconazole may be successful.

Pythiosis

Originally referred to as *phycomycosis*, pythiosis, a granulomatous disease, is caused by a number of taxonomically diverse nonseptated hyphal *Oomycetes*. The cell wall of *Oomycetes* differs from that of true fungi; hence antifungal agents are often ineffective against infections caused by these organisms. No antifungal agent has proved efficacious against this organism.

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Antiviral Therapy

12

Dawn Merton Boothe

INTRODUCTION
VIRAL REPLICATION AND TARGETS FOR ANTIVIRAL DRUGS
ANTIVIRAL DRUGS
Antiherpesvirus Drugs
  Pyrimidine Nucleosides
  Purine Nucleosides
  Miscellaneous Antiherpes Drugs
Antiretroviral Drugs
  Zidovudine
  Didanosine
Miscellaneous Antiviral Drugs
  Amantadine
  Suramin
  Inosiplex
  Interferon and Its Inducers
TREATMENT OF SELECTED VIRAL INFECTIONS
Treatment of Selected Canine Viral Infections
  Canine Parvoviral Enteritis
  Canine Distemper
  Infectious Canine Hepatitis
  Canine Infectious Tracheobronchitis
Treatment of Selected Feline Viral Infections
  Feline Panleukopenia
  Feline Infectious Peritonitis
  Feline Respiratory Disease
  Feline Viral Neoplasia
  Feline Immunodeficiency Virus

INTRODUCTION

The development of drugs intended to prevent and treat viral diseases has been frustratingly protracted even though 60% of human illness in developed countries are caused by viruses. Despite the long and intensive search for effective antiviral drugs, there are very few compounds that have clinical applications. Currently, there are approximately 16 antiviral drugs approved for use in human medicine. To date, there are no antiviral drugs that have been approved for use in veterinary medicine. Unfortunately, unlike the situation with many other anti-infectious drugs, applications for human antiviral drugs in veterinary patients is limited because the etiologic agents of viral diseases vary so widely. In recent years, however, a trend has developed toward development of drugs effective in viral diseases that affect veterinary patients. A very significant factor in this trend has been the advent of the acquired immunodeficiency syndrome (AIDS) in humans. The search for effective drugs useful for viral-induced disease, particularly for treatment of retroviruses, has been explosive. The pathogenesis and clinical signs of AIDS are very similar to those of feline leukemia virus (FeLV)–induced disease in the cat, and an FeLV cat model is frequently used for investigations of AIDS or other retroviral-induced diseases. Thus, information regarding therapy for selected viral diseases, particularly in cats, can be expected to emerge more so than for other viral-induced diseases.

For a number of reasons, it is more difficult to develop effective antiviral drugs than other anti-infectious agents. Drugs that target the viral processes must penetrate host cells to be effective. Because of the mechanisms by which viruses replicate (i.e., through the host genome), drugs that are effective against viruses also are likely to negatively impact the normal pathways of the host, and most antiviral drugs subsequently are characterized by a narrow therapeutic window. Therapy is further complicated by viral latency, the ability of the virus to incorporate its genome into the host genome, with clinical infection becoming evident without re-exposure to the organism. Clinical signs during the stages of infection when viruses might be most conducive to pharmacologic therapy often are mild to absent, and the need for antiviral therapy is not recognized until viral response is unlikely. Selection of the most appropriate antiviral drugs is handicapped by the lack of broad-spectrum antivirals and the lack of rapid tests to identify the infecting virus. In vitro susceptibility testing of viruses requires sophisticated and expensive techniques such as cell cultures. In vitro inhibitory testing procedures have not been standardized, and results vary with the assay system, cell type, and viral inoculum. Additionally, results may not correlate with therapeutic efficacy of antiviral drugs (Hayden, 1995). The lack of correlation between in vitro testing and clinical efficacy reflects, in part, the requirement of some antiviral drugs for activation (i.e., metabolism generally by the host) (Hayden, 1995). Not only is the spectrum of antiviral drugs narrow, but additionally, a drug often targets a specific viral protein (usually a polymerase or transcriptase enzyme) involved in viral nucleic acid synthesis (Hayden, 1995). The limited mechanism of action tends to facilitate the development of antiviral resistance, which can occur rapidly, often reflecting substitution of only a single although critical amino acid in the target protein. Because drugs often inhibit only active replication, growth often resumes once therapy is discontinued. Finally, drugs often cannot eliminate nonreplicating or latent viruses, and effective antiviral therapy generally also depends on an effective immune response. In humans, however, chronic drug therapy can suppress reactivation of the disease caused by the virus.

Drugs that simply inhibit single steps in the viral replication cycle are virustatic and only temporarily halt viral replication. Thus, optimal activity of some drugs depends on an adequate host immune response. Some antiviral drugs may enhance the immune system of the host.

VIRAL REPLICATION AND TARGETS FOR ANTIVIRAL DRUGS

Viruses are composed of a core genome consisting of either double-stranded or single-stranded DNA or RNA surrounded by a protein shell known as a capsid. Some viruses are further surrounded by a lipoprotein membrane or envelope. Both the capsid and lipoprotein membrane may be antigenic. Viruses cannot replicate independently and must usurp the host metabolic machinery in order to replicate. As such, viruses are obligate intracellular parasites. The host's pathways of energy generation, protein synthesis, and DNA or RNA replication provide the virus with the means of viral replication. For some viruses, replication is initiated by viral enzymes (Hayden, 1995). DNA viruses include poxvirus, herpesvirus, adenovirus, hepadnavirus, and papillomavirus. RNA viruses include rubella virus, rhabdovirus (rabies), picornavirus, arenaviruses, arboviruses, orthomyxovirus, and paramyxovirus (canine distemper) (Table 12–1).

Viral replication occurs in four to five sequential steps (Fig. 12–1): host cell attachment and penetration; disassembly or uncoating resulting in release of viral genome; transcription of viral genome (or viral messenger RNA), dependent on virus-specified enzyme; translation of regulatory (early) or structural (late) viral proteins; post-translation modifications (e.g., proteolytic cleavage, myristoylation, glycosylation), assembly of virion components; and release of the virus generally by budding or cell lysis (Hayden, 1995). For DNA viruses, viral DNA is transcribed to host mRNA by host cell mRNA polymerase (or, for poxvirus, viral RNA polymerase). Replication of RNA viruses requires virion enzymes to synthesize mRNA. Alternatively, viral RNA may serve as mRNA. Host cells generally are not involved in the replication of RNA viruses. Retrovirues are unique in that they contain reverse transcriptase, an enzyme that makes a DNA copy of a viral RNA template. The DNA is then incorporated into the host genome (as a provirus) and subsequently transcribed into genomic RNA and mRNA for translation into viral proteins (Hayden, 1995).

Potential targets in the viral life cycle that might be pharmacologically inhibited are expressed during extracellular stages of viral infection (i.e., penetration), intracellular stages (i.e., replication, assembly, and viral release), and dissemination. Those expressed during extracellular stages include specific enzymes whose release is required for skin and mucosal barrier penetration by some viruses; specific cell receptors required for penetration by other viruses; and specific precursor "fusion" proteins that must be activated before cell penetration by some viruses. Antivirals that diminish penetration of host cells by the virus are more viral specific and thus not as inherently toxic as those that prevent viral replication by interfering with viral nucleic acid, DNA, and protein synthesis. Because cell penetration is enhanced by viral-induced immunosuppression, pharmacologic immunomodulation may also help prevent viral penetration (Carrasco, 1984). Classes of antivirals that target cell entry include soluble receptor decoys and antireceptor antibodies. Uncoating of the virus can be targeted by ion channel blockers, capsid stabilizers, and fusion protein inhibitors (Hayden, 1995).

Currently, targets expressed during intracellular stages of viral infection are the most common sites of pharmacologic intervention, which includes antiviral drugs as well as a number of other classes of drugs (e.g., immunomodulators). Viral replication depends on macromolecular synthesis (by the host) of viral genome and on genome replication, transcription, and translation. Classes of drugs that inhibit transcription include inhibitors of viral DNA or RNA polymerase, reverse transcriptase, helicase, primase, or integrase. Natural substances capable of inhibiting viral transcription and translation (e.g., interferon) are much more potent than synthetic compounds. Viral replication is targeted by antisense oligonucleotides and ribozymes. Many antiviral drugs are nucleoside or nucleotide analogues, which prevent viral replication by blocking nucleic acid metabolism (Fig. 12–2). Viral replication is so closely connected to vital functions of the host cell that agents capable of inhibiting viral replication usually injure host cells as well. Although such drugs are more likely to be broad in their antiviral spectrum, most also are potential

Table 12–1. Classification of Viral Infections

Infection	Causative Virus	Family	Viral Type
Canine distemper	*Morbillivirus*	Paramyxoviridae	SSRNA
Canine viral enteritis	Canine parvovirus-1		DNA
	Canine parvovirus-2		DNA
	Canine coronavirus	Coronoviridae	SSRNA
	Canine rotavirus	Reoviridae	DSRNA
Infectious canine hepatitis	Canine adenovirus-1		DNA
Infectious tracheobronchitis	Parainfloenza virus-1		SSRNA
	Canine adenovirus-1		DNA
	Canine adenovirus-2		DNA
Feline panleukopenia	Parvovirus		SSDNA
Feline infectious peritonitis	Feline coronavirus	Coronaviridae	SSRNA
Feline viral neoplasia	Retrovirus		
Feline immunodeficiency virus	Lentevirus		
Feline respiratory disease			
Rhinotracheitis virus	Herpesevirus		DSDNA
Calicivirus	Calicivirus		SSRNA
Rabies	*Lyssavirus*	Rhabdoviridae	RNA

Abbreviations: DSDNA = double-stranded DNA; DSRNA = double-stranded RNA; SSDNA = single-stranded DNA; SSRNA = single-stranded RNA.

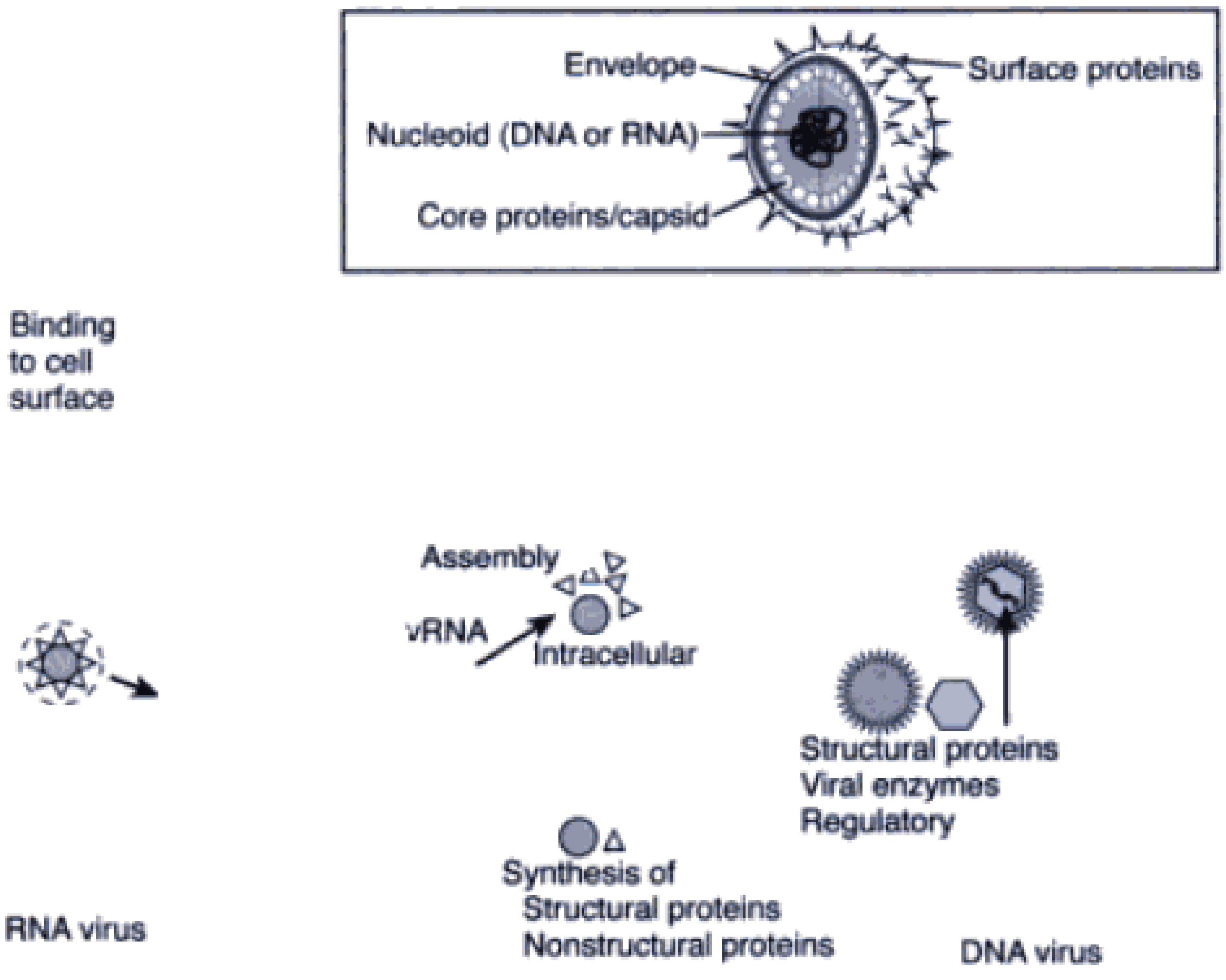


Figure 12–1. Replication of a representative RNA virus and DNA virus. mRNA = messenger RNA; vRNA = viral RNA.

teratogens, mutagens, and (particularly in humans) carcinogens and are associated with a variety of other host toxicities (Carrasco, 1984).

Fewer agents have been developed that block viral translation. Classes of drugs that inhibit viral translation include interferons, antisense oligonucleotides, and ribozymes. In addition, regulatory proteins might be inhibited. Another category of intracellular targets are specific enzymes, such as RNA or DNA polymerase, or reverse transcriptase of retroviruses—whose expression is required for the maintenance of the viral life cycle. Antiviral agents designed to block expression of these enzymes may have increased selectivity for viruses compared with the host, although their spectrum frequently is limited. Finally, assembly of synthesized viral macromolecules and release of the assembled virus may be pharmacologically inhibited. For example, interferon-induced inhibition of RNA tumor viruses occurs at assembly, although the mechanism is unknown (Carrasco, 1984).

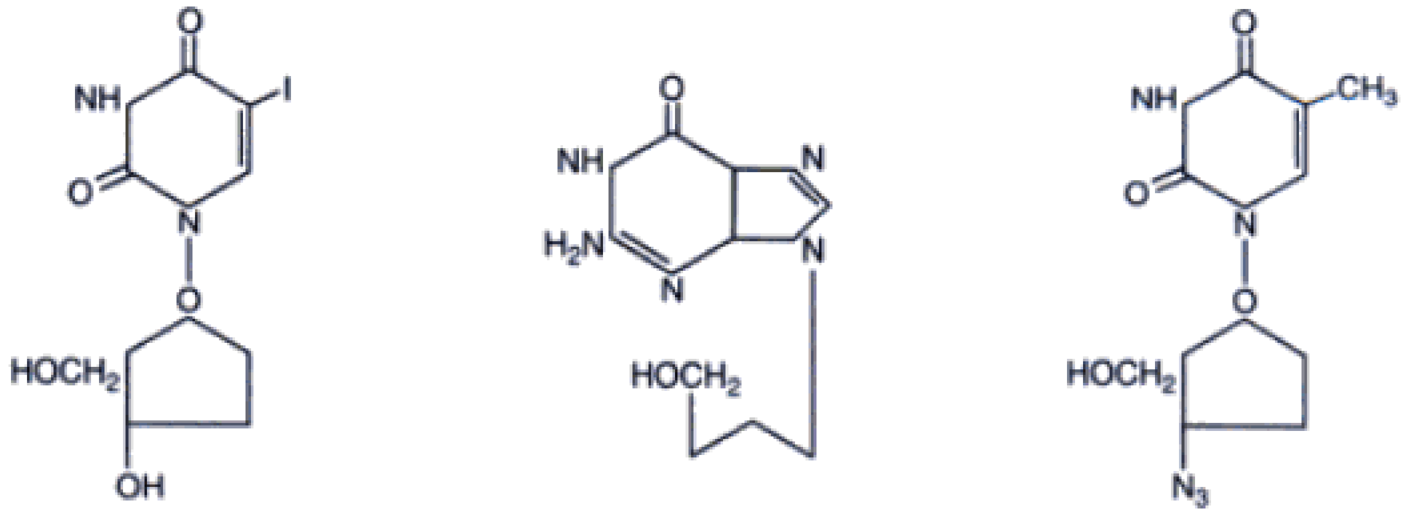
Post-translational modifications such as proteolytic cleavage may be targeted by some drug classes (e.g., protease inhibitors). Interferons and drugs that inhibit specific proteins target viral assembly. Finally, antiviral antibodies and cytotoxic lymphocytes target the release of viruses from the host cell.

The final stage of viral infection that may be pharmacologically inhibited is dissemination. Dissemination of some viruses appears to depend primarily on host immunosuppression by the virus. Thus, dissemination is another stage in which modulation of the immune system may help the host overcome viral infection (Carrasco, 1984).

Two categories of drugs have been and are currently being pursued for the pharmacologic treatment of viral diseases. Antiviral chemicals directly interfere with the virus, whereas biologic response modifiers stimulate the host's immune system, thereby increasing the host's ability to overcome viral invasion.

ANTIVIRAL DRUGS

Few antiviral drugs have been studied in animals, and widespread clinical use of antiviral drugs is not common in veterinary medicine. Only a selection of the more prom-



Idoxuridine Acyclovir Zidovudine

Figure 12–2. Structures of selected antiviral drugs. Structural similarity to host nucleotides results in limited host safety.

ising agents and their purported attributes are briefly discussed. Data regarding the drugs generally are extrapolated from information from human patients. Antiviral drugs are most practically categorized by the major viruses that are targeted. Many human antiviral drugs have not been studied or reported to be used for treatment of viral disorders in dogs or cats, and their inclusion in this chapter should not be interpreted as justification for use.

Antiherpesvirus Drugs

Pyrimidine Nucleosides

A variety of pyrimidine nucleosides (both halogenated and nonhalogenated) effectively inhibit the replication of herpes simplex viruses with limited host cell toxicity. The exact mechanism of action of these compounds appears to reflect substitution of pyrimidine for thymidine, causing defective DNA molecules.

Idoxuridine

Idoxuridine (5-iodo-2-deoxyuridine, IDU; Stoxil) was the first of the nucleoside analogues to prove useful in the treatment of viral diseases. Idoxuridine resembles and is substituted for thymidine. After phosphorylation, it is incorporated into both viral and host cell DNA. Altered DNA is susceptible to breakage, resulting in faulty transcription and altered viral proteins. The spectrum of antiviral activity is limited to DNA viruses, particularly members of the herpesvirus group. Resistance to IDU develops rapidly (Hayden, 1995). The ability of IDU to cause neoplastic changes, genetic mutation, and infertility limits its use to topical, primarily ophthalmic, infections. Idoxuridine is available as an ophthalmic ointment or solution. It is currently approved for use in the treatment of herpes keratitis in humans and has proved useful for the treatment of feline herpetic keratitis. One drop of a 0.1% solution is usually applied to the affected eye every hour; the 0.5% ointment can be applied every 2 hours (Dolin, 1987; Gustafson, 1986). Topical application of IDU to the conjunctiva has been associated with irritation, pain, pruritus, inflammation, and edema of the conjunctiva and punctate areas on the cornea. Resistance of viruses to the drug develops readily both in vitro and in clinical cases.

Trifluridine

Trifluridine (TFT; Viroptic) is a halogenated (fluorinated) pyrimidine that is similar and often considered superior to IDU. Trifluridine monophosphate irreversibly inhibits thymidylate synthetase, and TFT triphosphate competitively inhibits DNA polymerase incorporation of thymidine into DNA. Like IDU, it is preferentially incorporated into both viral and host DNA, and late virus-specific DNA transcription is inhibited (Hayden, 1995). Trifluridine has in vitro inhibitory effects against herpes simplex virus (types 1 and 2), cytomegalovirus, and selected adenoviruses. Clinical resistance to TFT has been reported. As with IDU, the primary therapeutic indication for TFT is herpetic keratitis. Trifluridine is prepared as a 0.1% ophthalmic solution and is usually applied six to eight times per day. Trifluridine is frequently preferred to IDU for the treatment of human and feline herpetic keratitis in order to avoid toxicities associated with IDU (Dolin, 1987; Gustafson, 1986). Adverse reactions include discomfort upon application and palpebral edema (Hayden, 1995).

Sorivudine

Sorivudine is a pyrimidine nucleoside analogue characterized by potency that results in a relative selectivity for varicella-zoster virus (VZV). The drug is initially phosphorylated by viral thymidine kinase and then metabolized to diphosphate by viral thymidylate kinase. As such, sorivudine triphosphate is a competitive inibitor of viral DNA replication. Unlike acyclovir, however, sorivudine is not incorporated into viral DNA. Inhibitory concentrations of sorivudine are 1000-fold lower for VZV than are those of acyclovir. Cellular uptake in cells infected with herpesvirus is 40-fold greater than in uninfected cells. Clinical resistance has not yet been detected (Hayden, 1995).

Sorivudine is well absorbed after oral administration and is characterized by 98% protein binding. The elimination half-life is 5 to 7 hours, although half-life increases with age. Elimination appears to be urinary, with minimal hepatic metabolism. Side effects are primarily gastrointestinal (nausea, vomiting, and diarrhea). Hepatic enzymes may increase. Long-term administration has caused hepatic neoplasms in rodents. Sorivudine (probably its metabolite) appears to negatively interact with 5-fluorouracil by inhibiting the enzyme responsible for fluorouracil metabolism (Hayden, 1995). Sorivudine is available in both oral and intravenous preparations but only as investigational drugs.

Purine Nucleosides

Certain purine nucleosides have proved to be effective antivirals and are used as systemic agents. Several of these antiviral drugs deserve special mention.

Vidarabine

Vidarabine (Vira-A) was initially investigated for its efficacy as a cancer chemotherapeutic drug. An analogue of adenine, vidarabine is phosphorylated by host enzymes and competitively inhibits viral DNA polymerase. It is substituted for adenine into DNA, thus inhibiting viral (and host) DNA polymerase. Mammalian DNA is also inhibited although to a lesser extent. Ribonucleoside reductase, RNA polyadenylation, and transmethylation reactions also are inhibited (Hayden, 1995). Vidarabine selectively inhibits DNA viruses, particularly herpesviruses. It is also effective against poxviruses, rhabdoviruses, hepadenaviruses, and selected RNA tumor viruses (Hayden, 1995). Until recently, the drug was prepared as an injectable suspension. It is poorly water soluble, however, and must be dissolved in large volumes of fluid before intravenous use. A 3% ophthalmic ointment is also available. Upon intravenous administration, vidarabine is deaminated to hypoxanthine arabinoside; the metabolite reaches concentrations that exceed the parent compound by 15-fold after constant intravenous infusion. The drug is eliminated renally but predominantly as the hypoxanthine metabolite. The elimination half-life of the metabolite is approximately 3.5 hours. Adverse reactions are more likely with intravenous administration and include gastrointestinal upset (vomiting, diarrhea) and central nervous system (CNS) derangements (hallucinations, ataxia, tremors, and painful peripheral neuropathies with long-term use). In addition, vidarabine is probably mutagenic and carcinogenic. Phlebitis, hypokalemia, rash, elevated transaminases, and pancytopenia as well as inappropriate concentrations of antidiuretic hormone have been reported in humans. Systemic use in humans is reserved for life-threatening infections (e.g., herpes encephalitis). Although vidarabine is preferred to IDU for topical therapy of herpetic keratitis, the advent of acyclovir has reduced its use. Vidarabine can be useful for patients that have developed resistance to acyclovir or in combination with acyclovir for life-threatening infections (Hayden, 1995). Literature regarding its use in the cat is limited (Dolin, 1987; Gustafson, 1986).

Acyclovir and Valacyclovir

Acyclovir is an acyclic synthetic purine nucleoside analogue that substitutes for guanosine in DNA synthesis. Valacyclovir is an L-valyl ester pro-drug of acyclovir. Efficacy of acyclovir depends on "activation" of the drug to its monophosphate derivative by viral thymidine kinase. Subsequent phosphorylation to the diphosphate and then triphosphate form is mediated selectively by cells infected with hepesvirus. The formation of acyclovir-GTP results in the inhibition of viral DNA polymerase and incorporation of acyclovir-GTP into viral DNA, which terminates viral DNA synthesis. The drug has a greater affinity for viral (vs. host) thymidine synthetase. Antiviral activity of acyclovir is limited essentially to herpesviruses. The in vitro activity of acyclovir is 100 times that of vidarabine and 10 times that of IDU. Viral resistance to acyclovir results from mutation to strains that are characterized by a reduction in viral thymidine kinase (the most common mechanism), altered substrate specificity, or altered viral DNA polymerase (Hayden, 1995).

Acyclovir is available in topical, oral (capsule), and parenteral (powder to be reconstituted) preparations. The bioavailability of the oral preparations (in humans) is poor (10% to 30%) and decreases with increasing doses (Hayden, 1995). In contrast, valacyclovir, which is rapidly and completely converted to acyclovir, increases bioavailability of acyclovir to 50%. Acyclovir distributes to all body fluids, including cerebrospinal fluid. It is eliminated primarily unchanged by glomerular filtration and tubular secretion and accumulates in patients with renal failure. The elimination half-life in adults with normal renal function is 1.5 to 6 hours; this can increase to 20 hours in anuric patients.

Toxicity of acyclovir, regardless of the preparation, is limited. Oral administration (of both acyclovir and valacyclovir) is associated with gastrointestinal upset. Intravenous administration may cause renal insufficiency and (rare) CNS side effects. Renal dysfunction is reversible and may reflect concentration in urine to the point that crystallization occurs (Hayden, 1995). Rapid infusion, dehydration, and inappropriate urine flow increase the risk of renal damage. Phlebitis also may accompany intravenous administration. Veterinary use of acyclovir may be limited, probably because of differences in viral thymidine kinase for acyclovir. In addition, antiviral resistance is increasing. Acyclovir is unable to eliminate latent infections. It is available as an ophthalmic ointment, a topical ointment and cream, an IV preparation, and various oral formulations. Another similar antiviral purine nucleoside analogue is ganciclovir, a synthetic guanine that is effective against human cytomegalovirus. Its mechanism of action is similar to that of acyclovir.

Famciclovir and Penciclovir

Like acyclovir, penciclovir is an acyclic guanine nucleoside. Its spectrum of activity (herpes simplex virus and VZV) is also similar to that of acyclovir. Penciclovir (up to 77% bioavailabe) is a pro-drug of famciclovir. Famciclovir is 100-fold less potent than acyclovir but is accumulated to higher concentrations than is acyclovir in infected cells (Hayden, 1995). Plasma elimination half-life approximates 2 hours, and elimination is renal. Although, like acyclovir, the drug is well tolerated orally, chronic administration appears to be tumorigenic, causing testicular toxicity in animals.

Ganciclovir

Ganciclovir is structurally similar to acyclovir, with the addition of a hydroxymethyl group on the acyclic side chain. Its spectrum includes herpesvirus with particular efficacy against cytomegalovirus; effective concentrations are 10-fold to 100-fold lower than the concentrations effective against other herpesviruses (Hayden, 1995). Unfortunately, similar concentrations are inhibitory to bone marrow progenitor cells. As with other guanine nucleosides, ganciclovir inhibits viral DNA synthesis after monophosphorylation mediated by viral thymidine kinase (herpes) or phosphotransferase (cytomegalovirus). Diphosphates and triphosphates of ganciclovir are formed by cellular enzymes. The triphosphate competitively inhibits deoxyguanosine triphosphate incorporation into both viral and host DNA, with preferential inhibition of viral over host DNA polymerase. Intracellular concentrations (which exceed acyclovir concentrations by at least 10-fold) decline much more slowly than those of acyclovir, resulting in a cellular elimination half-life of approximately 24 hours. Hence, the drug is given once daily (Hayden, 1995). Resistance most commonly reflects point mutations or deletions in viral DNA resulting in reduced formation of viral phosphotransferase.

Ganciclovir is poorly bioavailable (9%, with food). More than 90% of the drug is eliminated renally, with a (plasma as opposed to cell) elimination half-life of 2 hours. Elimination half-life increases proportionately with creatinine clearance. The primary adverse effect is myelosuppression, with neutropenia occuring in up to 40% and thrombocytopenia in 5% to 20% of patients. Myelosuppression more commonly occurs with intravenous administration and is generally reversible by 1 week after discontinuation of therapy, but can be persistent and fatal. Treatment with granulocyte colony-stimulating factor may minimize neutropenia (Hayden, 1995). The risk of myelosuppression is increased when ganciclovir is combined with other cytotoxic drugs. Side effects in the CNS also are frequent, occurring in up to 15% of human patients. Clinical signs include convulsions and coma. Other adverse effects have included infusion-related phlebitis, azotemia, anemia, fever, hepatic dysfunction, nausea, vomiting, and eosinophilia. Therapeutic use of ganciclovir includes cytomegalovirus retinitis, particularly in humans with AIDS-induced immunodeficiency. Ganciclovir is also used for treatment of any infection or prevention of infection (particularly in transplant recipients) associated with cytomegalovirus.

Ribavirin

Ribavirin (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide; Virazole) is a purine nucleoside analogue that is activated by viral phosphorylation and subsequently prevents the formation of mRNA and translation of viral genome (Dolin, 1987; Gustafson, 1986). The action of ribavirin involves specific inhibition of virus-associated enzymes, inhibition of the capping of viral mRNA, and inhibition of viral polypeptide synthesis. Thus, it is effective against both DNA and RNA viruses and is a broad-spectrum antiviral drug. Susceptible viruses include adenoviruses, herpesviruses, orthomyxoviruses, poxviruses, picornaviruses, rhabdoviruses, rotaviruses, and retroviruses. Viral resistance to ribavirin is rare. Ribavirin is well absorbed, widely distributed in the body, and eliminated by both renal and biliary routes as both parent drug and metabolites, and has a plasma half-life of 24 hours in humans. It does not have a wide margin of safety in domestic animals. Toxicity is manifested by anorexia, weight loss, bone marrow depression, anemia, and gastrointestinal disturbances. It has been successfully administered by topical, parenteral, oral, and aerosol routes. Ribavirin is administered as an aerosol to human patients afflicted with respiratory viral infections, thus avoiding the hematopoietic toxicities associated with systemic use of the drug. In the cat, in vitro investigations revealed marked antiviral activity against a strain of calicivirus but little efficacy for rhinotracheitis (Dolin, 1987; Gustafson, 1986). The use of ribavirin in the treatment of FeLV is currently under investigation.

Miscellaneous Antiherpes Drugs

Foscarnet

Foscarnet (phosphonoformic acid) is an inorganic trisodium salt that interferes directly with herpes viral DNA polymerase. The drug may also be effective in treating retroviral infections due to similar interference with reverse transcriptase. Direct actions preclude the need for intracellular activation. Foscarnet has a 100-fold greater affinity for viral as opposed to host DNA polymerase-α (Hayden, 1995). Point mutations in DNA polymerase are responsible for resistance. Foscarnet is poorly bioavailable after oral administration. The drug is concentrated in bones, resulting in complicated plasma elimination. Elimination (in humans) is bimodal with an initial 4- to 8-hour elimination half-life followed by a 3- to 4-day half-life. It is eliminated primarily by the kidneys, with clearance decreasing proportionately with creatine clearance.

Major side effects in human patients include nephrotoxicity and hypocalcemia, which can become symptomatic. Serum creatinine increases in up to 50% of patients but decreases after therapy is stopped. Acute tubular necrosis, crystalluria, and interstitial nephritis have occured. Sodium loading before therapy may decrease the risk of renal toxicity. Because foscarnet is highly ionized at physiologic pH, metabolic abnormalities are common in human patients. Calcium and phosphorus may decrease or increase. Decreases in ionized calcium may be sufficient to cause clinical signs consistent with tetany. Other CNS side effects reported in human patients (up to 25%) include tremors, irritability, seizures, and hallucinations. Fever, nausea, vomiting, anemia, leukopenia, and hepatic dysfunction also have been reported. Indications in human patients include cytomegalovirus retinitis and herpes infections that are resistant to acyclovir.

Foscarnet has been shown to be effective prophylactically in the treatment of feline rhinotracheitis. Its efficacy against retroviruses warrants further investigation for the treatment of FeLV. Currently, foscarnet is given to immunocompromised human patients and is being studied in the cat for treatment of retroviral infections.

Antiretroviral Drugs

Zidovudine

All clinically used (human-approved) antiretroviral agents are 2′,3′-dideoxynucleoside analogues. Zidovudine (AZT; Retrovir) is a thymidine analogue. Within the virus-infected cell, the 3′-azido group substitutes for the 3′-hydroxy group of thymidine. The azido group is then converted to a triphosphate form, which is used by retroviral reverse transcriptase and incorporated into DNA transcript (Dolin, 1987; De Clercq, 1987). The 3′ substitution prevents DNA chain elongation and insertion of viral DNA into the host cell's genome, preventing viral replication. Thus, the shared mechanism of action of these drugs is inhibition of RNA-dependent DNA polymerase (reverse transcriptase). This enzyme is responsible for conversion of the viral RNA genome into double-stranded DNA before it is integrated into the cell genome. Because these actions occur early in replication, the drugs tend to be effective for acute infections but relatively ineffective for chronically infected cells (Hayden, 1995). Cellular α-DNA polymerases are inhibited only at concentrations 100-fold greater than those necessary to inhibit reverse transcriptase, thus rendering this drug relatively safe to host cells. Cellular γ-DNA polymerase, however, is inhibited at lower concentrations.

Zidovudine is effective against a variety of retroviruses at low concentrations (<0.001 to 0.04 μg/mL). In contrast, suppression of (human) myeloid cells occurs at higher, albeit low, concentrations (0.3 to 0.6 μg/mL). The intracellular concentration time of AZT is 3 to 4 hours. Resistance to AZT is associated with point mutations resulting in amino acid substitutions in the reverse transcriptase. Prolonged use of AZT can facilitate viral resistance. The risk of resistance also appears to correlate with $CD4^+$ cell count and the state of infection. A return to susceptibility of the virus to AZT may occur after the drug has been discontinued for a period of time (Hayden, 1995).

In human patients, AZT is rapidly absorbed, with a bioavailability of 60% to 70%. Food impairs absorption. Concentrations in the cerebrospinal fluid approximate 50% of those in plasma. The plasma elimination half-life is 1 to 1.5 hours. In human patients, AZT undergoes first-pass metabolism. Although metabolites appear to be void of antiviral toxicity, at least one may contribute to myeloid toxicity. Granulocytopenia and anemia are the major adverse effects of AZT in human patients. The risk of toxicity increases in human patients with low (CD4$^+$) lymphocyte counts, high doses, and prolonged therapy. Granulocyte colony-stimulating factor is indicated for management of granulocytopenia. Central nervous system side effects are more likely as therapy is begun. Other side effects reported in humans include myopathy (characterized by weakness and pain), neurotoxicities, hepatitis (uncommon), and esophageal ulceration. Resolution of myopathy occurs slowly after drug therapy is discontinued. The risk of myelosuppression is increased by drugs that inhibit glucuronidation or renal excretion. Therapeutic indications for AZT in humans include treatment of human immunodeficiency virus (HIV) infections. Treatment with AZT prolongs survival, decreases the incidence of opportunistic infections, increases measures of immune function, and decreases HIV antigens and RNA. Zidovudine has been combined with didanosine or zalcitabine for more sustained CD4$^+$ lymphocyte response.

Studies in cats regarding the efficacy of AZT (10 to 20 mg/kg twice daily for 42 days) for FeLV infection indicated that AZT prevents retroviral infection if administered immediately after virus exposure and may reduce replication if administered to previously infected animals (Cogan, 1986). Serum-neutralizing antibodies developed in some of the infected cats, and the cats became resistant to subsequent viral challenge. There was no altered progression of disease in cats for whom treatment was withheld until day 28 postinfection, although the level of viremia was much lower than in untreated cats. Zidovudine appeared to be nontoxic in uninfected cats, although 3 of 12 infected kittens became anorectic and icteric and were vomiting after 40 days of treatment. Zidovudine may cause Heinz body anemia (Sellon, 1998). Complete blood counts should be performed on cats receiving AZT.

Didanosine

Didanosine is a purine nucleoside effective against HIV, including strains that have developed resistance to AZT. Although it is 10- to 100-fold less potent than AZT, it is more active in quiescent cells and in nondividing (human) monocytes and macrophages. It also is not toxic for hematopoietic precursor cells or lymphocytes at clinically relevant concentrations. It is metabolized inside the cell to its active derivative (ddATP), which competitively inhibits virus preferentially to host reverse transcriptase. Oral bioavailability of didanosine is about 40% in humans. Because it is very acid labile, food decreases absorption by 50% or more. Didanosine is available as both tablets and powder, with the tablet being 20% to 25% more bioavailable than the powder. Only about 20% of drug in plasma distributes to the cerebrospinal fluid. Up to 60% of the drug is excreted unchanged through the kidneys, with a plasma elimination half-life of up to 1.5 hours. Intracellular metabolism may be responsible for some plasma elimination. Side effects include painful peripheral neuropathy and pancreatitis. High doses increase the risk for both. A history of pancreatitis predisposes the patient to this side effect. Up to 70% of human patients develop pancreatitis, although hyperamylasemia will occur in up to 20%. Other adverse effects include diarrhea, rashes, CNS signs including insomnia and seizures, optic neuritis, and, rarely, hepatic failure or cardiac dysfunction. Animal studies also have found gastrointestinal, bone marrow, hepatic, and renal dysfunction. Didanosine is approved for treatment of advanced HIV infections in human patients intolerant of or resistant to AZT. Stavudine, a thymidine nucleoside, and zalcitabine, a cytosine nucleoside, are alternatives to AZT therapy for human patients (Hayden, 1995).

Miscellaneous Antiviral Drugs

Amantadine

Amantadine and its derivative rimantadine are synthetic antiviral agents that appear to act on an early step of viral replication after attachment of virus to cell receptors. The effect seems to lead to inhibition or delay of the uncoating process that precedes primary transcription. Amantadine may also interfere with the early stages of viral mRNA transcription. Amantadine at usual concentrations inhibits replication of different strains of influenza A virus, influenza C virus, Sendai virus, and pseudorabies virus. It is almost completely absorbed from the gastrointestinal tract, and about 90% of a dose administered orally is excreted unchanged in the urine over several days (human data). The main clinical use has been to prevent infection with various strains of influenza A viruses. In humans, however, it also has been found to produce some therapeutic benefit if taken within 48 hours after the onset of illness. Amantadine and its derivatives may be given by the oral, intranasal, subcutaneous, intraperitoneal, or aerosol routes. It produces few side effects, most of which are CNS related; stimulation of the CNS is evident at very high doses.

Suramin

Suramin is a polysulfonate hexasodium salt capable of inhibiting reverse transcriptase. Suramin is currently being investigated for its efficacy in the treatment of FeLV. One study (Cogan, 1986) evaluated the efficacy and safety of suramin (10 to 20 mg/kg) in two FeLV-infected cats. Although toxic signs were limited to vomiting and anorexia (both resolving between treatments), viremia in both peripheral blood cells and serum did not resolve. Serum viral infectivity transiently decreased during treatment but was significantly higher 14 days after treatment was discontinued. Previous in vitro studies by the same author revealed a 90% inhibition of infectivity at drug concentrations of 100 mg/mL.

Inosiplex

Inosiplex (Isoprinosine) is a compound formed from inosine and the para-acetamidobenzoate salt of 1-dimethylamino-2-propanol. Inosiplex can inhibit cytopathic effects of several viruses in culture. In vivo experiments, however, suggest that optimal activity of inosiplex occurs with therapeutic administration after viral infection and requires an adequate host immune response. The mechanism of antiviral activity appears to involve specific suppression of viral mRNA. Inosiplex does not appear to be as efficacious as several antimetabolite antiviral compounds. Inosiplex can also induce T-cell differentiation similar to that induced by thymic hormones, apparently by augmenting RNA synthesis. Thus, inosiplex may be more useful as an immunopotentiator in immunodeficient patients (see earlier discussion of biologic response modifiers) (Dolin, 1987; De Clercq, 1987, Taveres et al., 1987).

Several drug classes continue to be investigated mainly because of their in vitro antiviral activities. Their potential clinical usefulness remains obscure in most instances. Included among these agents are thiosemicarbazones, guanidine, zidovudine (azidothymidine), benzimidazoles, arildone, phosphonoacetic acid, rifamycins and other antibiotics, and several natural products.

Interferon and Its Inducers

Interferons (see also Chapter 20) are a group of inducible cellular glycoproteins that interact with cells and render them resistant to infection by a wide variety of RNA-containing and DNA-containing viruses. In addition, interferons have numerous other effects on target cells, including a reduction in the rate of cell proliferation and alterations in the structure and function of the cell surface, the distribution of cytoskeletal elements, and the expression of several differentiated cellular functions. Interferons induce the synthesis of new proteins that are responsible for the activation of cellular endonucleases that degrade viral mRNA. Human interferons are classified as α, β, or γ, depending on their physical stability, immunologic neutralization properties, host range, and homology in amino acid sequence. Those used in clinical trials have been produced by induction of synthesis by human white blood cells, fibroblasts, lymphoblasts, and, more recently, recombinant DNA techniques in bacteria. Numerous modes of antiviral action have been proposed: In addition to their ability to establish an antiviral state in host cells, they also appear to modulate the immune system of the host.

Interferons inhibit the replication of a wide variety of viruses. Among the RNA-containing viruses, the togaviruses, rhabdoviruses, orthomyxoviruses, paramyxoviruses, reoviruses, and several strains of picornaviruses and oncornaviruses are sensitive to inhibition by interferons. Among the DNA-containing viruses, the poxviruses and several strains of herpes simplex types 1 and 2 viruses, as well as cytomegalovirus, are inhibited by interferons. Adenoviruses are generally resistant. There are extreme variations in sensitivity to interferons among different types and even strains of virus. In addition, the responses in different model and test systems can be extraordinarily variable. Interferons appear not to be as useful in the therapy of viral infections as was hoped initially. A native human lymphokine preparation containing an interferon has been useful against infectious bovine rhinotracheitis (IBR) in feeder calves under some circumstances; it appears to reduce virus excretion during infection, tempers the pyrexia associated with IBR, and may improve average daily weight gain. Interferons are usually administered parenterally but recently also have been used orally with some success. Although rare at recommended dosages, side effects may occur at higher levels.

Several substances induce interferon and have been tested for the prevention and treatment of viral infections and for treatment of neoplastic diseases. Although effective in some model systems, interferon inducers have not yet been found to be clinically useful because of their toxicity. High-molecular-weight inducers include polyriboinosinic acid/polyribocytidylic acid or poly (I)/poly (C); low-molecular-weight inducers include tilorone, aminobromophenylpyrimidinone, and aminoiodophenylpyrimidinone.

TREATMENT OF SELECTED VIRAL INFECTIONS

Treatment of viral diseases in small animals is nonspecific and seldom includes antiviral drugs. Therapy tends to be supportive, focusing on fluid and electrolyte supplementation, prevention or treatment of secondary bacterial infection, and treatments that support the function and structure of the organ targeted by the infection. By far, the most important approach to management of viral diseases in dogs and cats is prevention and, in particular, an effective vaccination program. In addition, isolation of infected animals and cleansing of environments contaminated with potentially infecting viruses is important to limiting the spread of viral infections.

Treatment of Selected Canine Viral Infections

Canine Parvoviral Enteritis

Parvoviral enteritis, caused by canine parvovirus-2 (CPV-2), is among the most common and fatal viral infections afflicting dogs, including most members of the family Canidae. Infection by this highly contagious virus generally reflects contact with infected feces. Animals, humans, and objects can serve as vectors. After exposure, viral replication begins in the lymphoid tissue of the gastrointestinal tract from where it disseminates to the intestinal crypts of the small intestine. The virus localizes in the epithelium of the tongue, oral and esophageal mucosa, small intestine, and lymphoid tissue. Because CPV-2 infects the germinal cells of the intestinal crypt, cell turnover is impaired and villi shorten. Mitotically active myeloid cells and lymphoid cells are also targeted, leading to neutropenia and lymphopenia. Complications of intestinal damage include bacteremia, endotoxemia, and disseminated intravascular coagulation (DIC). Infections are most severe in puppies less than 12 weeks of age due to their immature immune system. Clinical signs include vomiting (which can be severe), diarrhea, and anorexia. Animals may be febrile. Clinical pathology may reveal leukopenia. Myocarditis can develop in patients infected in utero or less than 8 weeks of age. Diagnosis is based on clinical signs, leukopenia (generally proportional to the severity of illness), and enzyme-linked immunoassay (ELISA) antigen testing.

Therapy for canine parvoviral enteritis is symptomatic and focuses on restoration of fluids and electrolytes and on prevention or treatment of bacteremia or endotoxemia. Fluid therapy is the single most important treatment and should be aggressive and continued as long as the patient is vomiting and diarrhea is present. Among the antiemetics, metoclopramide is most successful, although ondansetron should be considered for animals that fail to respond. Treatment of diarrhea is generally not indicated. The use of narcotic motility modifiers (e.g., loperamide, diphenoxylate) has been recommended if necessary (Hoskins, 1998), but their use may prolong the presence of undesirable toxins in the gastrointestinal luman. Thus, their use is discouraged. Antimicrobial therapy should focus on both gram-negative coliforms and anaerobic organisms. In general, an injectable β-lactam combined with an aminoglycoside have proved efficacious. Fluid therapy, once-daily dosing, and the immature nature of pediatric canine kidneys provide protection against aminoglycoside-induced renal disease. Fluorinated quinolones should be avoided if possible because of the risk of cartilage damage. Ceftiofur has been used because of its potential for intravenous administration and its efficacy against *Escherichia coli*, one of the major contributors to secondary bacterial complications of parvovirus. Note, however, that efficacy and safety at doses necessary to control the systemic bacterial complications of parvovirus have not been documented. In addition, efficacy against anaerobic organisms of the gastrointestinal tract has not been studied.

Parvoviruses are extremely stable, being resistant to environmental conditions and many chemical disinfectants. Canine parvovirus is susceptible to sodium hypochlorite (1 part household bleach to 30 parts water). Exposure to diluted bleach must be long.

Canine Distemper

Canine distemper (Greene and Appel, 1998) spreads by aerosolization to the epithelium of the upper respiratory tract. Multiplication in tissue macrophages leads to spread to lymphatics, tonsils, bronchial lymph nodes, and, ultimately, to lymphatic tissues of the gastrointestinal tract, liver, and other organs. Additional spread generally is hematogenous. Leukopenia characterized by lymphopenia develops as the virus proliferates in lymphoid tissues. Animals with adequate immunity are able to clear infection within 8 to 9 days. In dogs with an insufficient immune response, the virus spreads to other tissues, including the skin and other organs. Persistent viral infection of the CNS appears to develop in dogs that are not able to generate circulating IgG antibodies to the viral envelope. Immune complex deposition in the CNS may facilitate viral infection. Lesions and their sequelae in the CNS vary with the age and immunocompetence of the dog, the pathogenicity of the virus, and the duration (acute vs. chronic) of infection. Acute encephalitis is more likely in young or immunosuppressed dogs and reflects direct viral damage. Demyelination polioencephalomalacia is characterized by minimal inflammation. Continued infection in the CNS leads to progressive increases in the immune response, ultimately contributing to continued and widespread damage. Chronic infection is associated with increased concentrations of antimyelin antibodies, activation of macrophages, and release of reactive oxygen radicals. Despite resolution of inflammation in surviving animals, canine distemper virus can persist in infected brain tissues.

Clinical signs vary with the extent of infection and include general listlessness, fever, upper respiratory tract infection (similar to kennel cough), keratoconjunctivitis sicca, serous to mucopurulent discharge, and vomiting and diarrhea, often associated with tenesmus. Animals may become severely dehydrated. Neurologic signs generally develop after recovery (generally at 1 to 3 weeks but can be up to several months) and tend to be progressive. Mature animals can abruptly develop neurologic signs despite prior vaccination and no previous evidence of disease. Clinical signs of CNS involvement vary with the area of the CNS affected and with the magnitude of damage and include hyperesthesia, cervical rigidity, seizures, cerebellar signs, paraparesis or tetraparesis, and myoclonus. Diagnosis is based on immunologic testing of IgM (ELISA). Measurements of IgG in both serum and cerebrospinal fluid may be useful for detecting chronic CNS infections. Immunocytology may also be helpful in the diagnosis of canine distemper, although the need for special equipment renders this aid less practical.

The most appropriate approach for limiting morbidity and mortality associated with canine distemper is proper vaccination (Greene and Appel, 1998). Treatment continues to be largely supportive and focuses on prevention or treatment of bronchopneumonia (usually caused by *Bordetella bronchiseptica*), fluid and electrolyte support with supplementation of B vitamins as needed, and treatment of neurologic signs. Progression of neurologic signs may provide justification for treatment of cerebral edema (e.g., single administration of dexamethasone) (Greene and Appel, 1998). Seizures should be treated with anticonvulsant medications (diazepam for immediate control, phenobarbital or bromide for long-term control). Myoclonus is not treatable. Chronic inflammatory forms of distemper (including optic neuritis, encephalitis) may require long-term glucocorticoid therapy. Glucocorticoids that are more effective in their ability to control oxygen radicals (e.g., methylprednisolone) may offer an advantage, although this has not be clinically addressed with controlled studies. Therapy with ascorbic acid intravenously has not been proved to be clinically useful but nonetheless, has been recommended (Greene and Appel, 1998). Infections associated with measles in children apparently have responded favorably to two treatments with vitamin A (200,000 IU or 60 mg) if given within 5 days of the onset of clinical signs (Greene and Appel, 1998). Canine distemper virus is extremely susceptible to common disinfectants.

Infectious Canine Hepatitis

Infectious canine hepatitis (Greene, 1998a) initially localizes in the tonsils and spreads to regional lymph nodes and then to the bloodstream. The virus rapidly disseminates to all tissues, with hepatic parenchymal cells and vascular endothelial cells serving as the primary targets. Cytotoxic effects of the virus cause injury to the liver, kidney, and eye. In immunocompetent animals, infection is cleared within 7 days. Acute hepatic necrosis tends to develop in immunoincompetent animals. Although acute necrosis is the most common cause of death in animals surviving the intial phases of infection, it also can be self-limiting. Animals that respond with a partial neutralizing antibody tend to develop chronic active hepatitis, which can progress to fibrosis. Although renal lesions may develop with acute infection, progression to chronic renal disease apparently does not occur. Animals, however, remain prone to pyelonephritis. Ocular location of the virus occurs in about 20% of animals and can cause severe anterior uveitis and corneal edema. Ocular lesions tend to be self-limiting unless complications develop. Disseminated intravascular coagulopathy is a frequent acute complication of infectious canine hepatitis, probably triggered by widespread endothelial damage and activation of the clotting cascade. Decreased hepatic function and inability to clear products of degradation and synthesize clotting factors contribute to DIC. Clinical signs in the acute stages of infectious canine hepatitis include enlargement of lymphoreticular tissues, fever, coughing, abdominal tenderness associated with hepatomegaly, and hemorrhagic diathesis. Less commonly, icterus and CNS signs may develop. Ocular lesions may be associated with blepharospasm, photophobia, cloudiness of the cornea, and ocular discharge. Diagnosis is based on clinical laboratory changes consistent with damage caused by infectious canine hepatitis and serologic testing.

Therapy is supportive and should continue until the liver has adequately healed from acute damage. Therapy focuses on fluid and electrolyte support, treatment as indicated for DIC (including both replacement therapy and anticoagulant therapy), and treatment for hepatic encephalopathy as needed in acute stages. Hypertonic glucose (0.5 mL/kg of a 50% solution given intravenously over 5 minutes) may be helpful in the presence of hypoglycemia. Polyinosinic-polycytidylic acid, an interferon inducer, has been used experimentally but is not a practical therapy. Persistence of chronic liver disease should be treated as is appropriate.

Infectious canine hepatitis is very resistant to many chemical disinfectants, including chloroform, ether, acid, and formalin. Chemical disinfectants that appear to be useful include iodine, phenol, and sodium hydroxide. The application of steam (5 minutes at 50° to 60°F) may be a reasonable method of disinfection for instruments.

Canine Infectious Tracheobronchitis

The most common causative organisms of kennel cough are canine parainfluenza virus, a single-stranded RNA virus, and *B. bronchiseptica* (Ford and Vaden, 1998). Other viruses and bacterial infections are also associated with the syndrome. Bacterial causes of tracheobronchitis are discussed in Chapter 10. Viral transmission occurs primarily by aerosol or, for some viruses, by oronasal contact. The lack of viral replication in macrophages limits infection of the virus to the upper respiratory tract, although it is the viral-induced damage to the respiratory epithelium that allows secondary bacterial infection. *B. bronchiseptica* preferentially attaches to the respiratory epithelium, replicates on respiratory cilia, and releases potent toxins that impair phagocytosis and cause ciliostasis, allowing infection by opportunistic organisms. The most common clinical signs associated with canine infectious tracheobronchitis (ITB) is paroxysmal nonproductive coughing, often associated with retching. Edema of the vocal folds is responsible for the characteristic "honking" sound of the cough. History includes exposure to other dogs, often at a boarding facility. Diagnosis is based on history and clinical signs. Culture of the upper airways (via bronchoscopy or transtracheal wash) can support diagnosis of a bacterial component. Rising antibody titers may be helpful in indentifying a specific viral etiology. Therapy focuses on control of cough and, in cases complicated by persistent bacterial infection, antimicrobials. Glucocorticoids may be helpful for controlling cough but do not appear to shorten the clinical outcome. Antitussive therapy should include both peripheral bronchodilators and centrally active drugs. Narcotic derivatives are more likely than non-narcotics to control cough associated with ITB. Aerosol therapy may be helpful in cases associated with marked accumulation of respiratory secretions or pneumonia. Mucolytics, such as *N*-acetylcysteine, may be very irritating to the respiratory tract and can be given orally or parenterally.

Parainfluenza virus is susceptible to sodium hypochlorite, chlorhexidine, and benzalkonium solution. Control of outbreaks in a kennel may require isolation of the entire facility for up to 2 weeks. Vaccines are available; intranasal vaccination may lead to clinical signs typical of ITB.

Treatment of Selected Feline Viral Infections

Feline Panleukopenia

Feline panleukopenia (Greene, 1998b) is caused by parvovirus transmitted by direct contact between cats or between cats and vehicles acting as vectors. As with other parvoviruses, cells that are rapidly dividing are particularly susceptible to infection, including bone marrow, lymphoid tissue, and intestinal mucosal crypt cells. In utero infection can cause a number of reproductive disorders in the pregnant cat, ranging from loss of fetuses if infection occurs early in the pregnancy to birth of affected kittens. Injuries in kittens occur in the CNS, particularly the cerebellum, optic nerve, and retina. Panleukopenia causes acute signs, including fever, depression, anorexia, and, less frequently, vomiting. Dehydration can be extreme. Other potential clinical signs include ulceration, bloody diarrhea and icterus, and signs indicative of DIC. Queens infected during pregnancy may be diagnosed with infertility, and dead fetuses may mummify. Kittens affected in utero present with classic signs of cerebellar hypoplasia.

Diagnosis generally is based on a complete blood count. Therapy is symptomatic and focuses on fluid and electrolyte replacement (with vitamin B) and maintenance, antiemetics (generally metaclopramide), and broad-spectrum antibiotics to control secondary infection. Diazepam or other appetite stimulants can be attempted in anorectic cats that are not vomiting. Blood transfusions may be indicated in the presence of severe anemia.

Feline Infectious Peritonitis

Feline infectious peritonitis (FIP; Addie and Jarrett, 1998) is caused by coronaviruses after ingestion and possibly inhalation of the virus. Transmission appears to be direct through feces or saliva, mutual grooming, and close contact. Enterocytes contain a receptor for the virus, and replication apparently takes place in the gastrointestinal epithelium. Immune complexes that form in response to the virus or the specific viral antigen include both antiviral antibodies and complement. Activation of complement leads to the release of vasoactive amines, endothelial retraction, and increased epithelial permeability, which in turn allows exudation of the protein-rich exudate typical of FIP. Neutrophil accumulation and subsequent release of lysozymes cause vascular necrosis. Systemic involvement may reflect spread of viral-infected macrophages and subsequent complement activation or deposition of immune complexes from circulation into tissues. Pyogranulomata develop, the magnitude of which reflects the size, number, and amount of antibody and antigens. Regions of high blood pressure and turbulence appear to be more common sites of deposition. Clinical signs of FIP thus vary with the site of virus and immune complex deposition and generally reflect either an effusive or noneffusive form. Effusive FIP causes ascites with or without pleural effusions. Noneffusive FIP tends to be vague in presentation and includes fever, weight loss, anorexia, and depression. Ocular lesions are common, characterized by iritis, hypopyon, and hyphema. Pyogranulomata may be present in the vitreous or the retina. Neurologic signs are not uncommon and include ataxia, nystagmus, and seizures. Meningitis may lead to tremors, hyperesthesia, behavioral changes, or cranial nerve defects. Hydrocephalus also may develop. Diagnosis can be confirmed only by immunohistochemical or immunofluorescent staining of intestinal biopsy tissue. Clinical pathologic changes and serology, however, provide support for the diagnosis.

Treatment of FIP is controversial. Treatment of cats with clinical signs is largely palliative and focuses on improving the quality of life, generally by controlling the immune response. Although glucocorticoids in seropositive cats may decrease the development of immune complex disease and thus the inflammatory sequelae, they also may cause immunosuppression and subsequent precipitation of FIP. Treatments have included immune-suppressive doses of prednisolone and cyclophosphamide; or melphalan (2 mg/m^2 or one fourth of a 2-mg tablet orally every 48 hours) or chlorambucil (20 mg/m^2 every 2 to 3 weeks, orally), interferon (human alpha) (2×10^6 IU/kg per day intramuscularly for the effusive form and 30 IU/kg per day for 7 days on/7 days off for the noneffusive form), and supportive drugs. Supportive therapy includes fluids as necessary, antibiotics, ascorbic acid, vitamin B, and vitamin A.

Coronavirus can be removed from the environment with chemical disinfection using diluted (1:32) sodium hypochlorite solution.

Feline Respiratory Disease

Feline rhinovirus and calicivirus are the major viral causes of respiratory disease in the cat (Gaskell and Dawsohn, 1998), but a number of bacterial organisms contribute to the pathogenesis, including *B. bronchiseptica*, *Mycoplasma* species, and *Chlamydia psittaci*. Other viral organisms (e.g., reovirus, poxvirus) also may contribute. Rhinovirus is a herpesvirus. Natural routes for both viral infections are via the nasal, oral, and conjunctival mucosa. Viral replication of rhinovirus occurs primarily in the nasal mucosal epithelium and, for calicivirus, throughout the respiratory epithelium. Growth of rhinovirus tends to be restricted to areas of lower body temperature; thus, lesions tend to be limited to the nasal mucosa and the pharynx. Lesions reflect necrosis and result in the typical clinical signs of marked sneezing, pyrexia, depression, and anorexia. Cats may salivate. Conjunctivitis with chemosis and hyperemia are common, with mucopurulent discharge of the nares and eyelids developing. Oral ulceration is rare. Damage to nasal turbinates can be extensive and permanent, leaving the infected cats susceptible to chronic upper respiratory tract infections (e.g., rhinitis, sinusitis) and conjunctivitis. Calicivirus infection has variable clinical signs because it is more likely to infect the lungs. Oral lesions (tip of the tongue, mouth, and nose) are the most predominant sign, reflecting epithelial necrosis; fever and mild respiratory and conjunctival signs also occur. Feline calicivirus also has been associated with chronic gingivitis/stomatitis. Sneezing and ocular and nasal discharge are not as common as with rhinovirus. Pulmonary lesions begin with alveolitis. Lameness also may occassionally develop.

With the exception of ocular rhinovirus infection, treatment of feline viral respiratory diseases is supportive. Ocular herpetic infections can be treated topically with a number of antiviral drugs. Examples include, in order of efficacy, trifluridine (1%), idoxuridine (0.1%), vidarabine (3%), and acyclovir (3%). Each must be applied at 4-hour intervals for 1 week beyond the resolution of clinical signs (Martin, 1998). Interferon-α_2 (300,000 IU vial reconstituted in artificial tears) can also be used (topical regimen as with antiviral drugs), although its efficacy is not known. Supportive therapy should include antimicrobials (e.g., fluorinated quinolones, doxycycline) that target presumed or known infecting bacterial organisms. Oral medication may be difficult to administer; injections and medications that can be given once daily thus may be preferred. Nasal decongestants may be helpful during the acute phases, but note that α-adrenergic decongestants may contribute to nasal mucosal necrosis due to impaired blood flow. Antihistaminergic products are probably preferred. Mucolytic drugs and mucokinetics may facilitate movement of accumulated respiratory secretions. *N*-acetylcysteine can be given via injection rather than orally. Aerosolization also may be helpful because lesions tend to predominate in upper airways.

Feline Viral Neoplasia

Feline leukemia virus (FeLV) is caused by an oncornavirus subfamily of retroviruses. Viral replication depends on the presence of reverse transcriptase (RNA-dependent DNA polymerase). The enzyme makes a provirus (a copy of DNA) that is subsequently inserted into the host genome. The binding site of FeLV is the major envelope glycoprotein (gp70); antibodies to this envelope provide protective immunity. Malignant cells also contain the feline oncornavirus cell membrane antigen (FOCMA); high levels of FOCMA antibodies render the cat resistant to viral-induced leukemia or lymphoma. FeLV is contagious, with transmission occurring via the saliva after close contact between cats. Iatrogenic transmission can occur through contaminated blood or instruments that penetrate (e.g., needles) Initial infection is characterized by malaise and lymphadenopathy. Cats that mount an adequate immune response recover. Feline leukemia virus spreads hematogenously to the bone marrow in cats that do not mount an immune response. Cats can become latently infected, with the virus residing undetected (by ELISA, fluorescent antibody testing, or viral culture) in the bone marrow.

Cats infected with FeLV die due to viral-induced neoplasia (lymphoma or leukemia), suppression of the bone marrow (anemia), or infections caused by FeLV-induced immunosuppression. Bone marrow suppression occurs because FeLV can block differentiation of erythroid progenitors. Other mechanisms may also be involved. Platelet and leukocyte abnormalities also may occur, and a "panleukopenia-like" syndrome has been described induced by FeLV. Immunosuppression reflects disruption of T-cell function, ultimately impacting both cellular and humoral immunity. Immune complex disease has been described and can be induced experimentally with antibodies to gp70. Glomerulonephritis may be a sequela. Other disorders include those of the reproductive tract (infertility, abortions, endometritis), lymphadenopathy (most severe in submandibular lymph nodes), osteochondromas, and olfactory neuroblastomas. Diagnosis of FeLV is based on fluorescent antibody testing and ELISA. The indications and advantages for each are described elsewhere (Cotter, 1998).

Treatment of FeLV-related diseases varies with the syndrome resulting from the infection and, for most syndromes, has been discussed in other chapters. Lymphoma is generally fatal within 1 to 2 months if not treated. Prognosis for complete remission is relatively good for the otherwise healthy cat (Cotter, 1998). Treatment focuses on combinations of chemotherapeutic drugs and, for selected cancers (e.g., nasal lymphoma), radiation therapy. Single-agent glucocorticoids are relatively ineffective and are palliative only. The most commonly used combination of chemotherapeutic agents is cyclophosphamide, vincristine, and prednisone. Other drugs that might be added to this regimen, depending on the cell type and response, include doxorubicin and, less commonly, L-asparaginase, cytosine arabinoside, and methotrexate. Antiemetics may be necessary, as might appetite stimulants (cyproheptadine, diazepam, megestrol acetate).

Acute leukemia tends to be less responsive. Cotter (1998) reports a 25% remission rate for acute lymphocytic leukemia when vincristine and prednisone are used but no survival in cats with acute myelogenous leukemia when doxorubicin or cytosine arabinoside is used. Bone marrow suppressive disease is treated with repetitive blood transfusions. Previously seropositive cats have converted to seronegative (ELISA negative) status after blood transfusions, generally after the first treatment. Prednisolone may increase the life span of erythrocytes if immune-mediated destruction is contributing to anemia. Human recombinant (and, when available, canine recombinant) growth factors may be useful for increasing bone marrow production of precursor cells despite the fact that most animals with anemia have high endogenous concentrations. Response to human recombinant erythropoietin (100 U/kg, subcutaneously three time weekly) requires about 3 to 4 weeks. This product should be reviewed before its use. Likewise, recombinant granulocyte colony-stimulating factor may be of benefit in the treatment of leukopenias. Development of antibodies to both of these products may limit their use beyond several weeks.

No antiviral drug has been shown to clear a FeLV viremic cat. Drugs that target reverse transcriptase, such as AZT, offer the most promise for effective therapy. Zidovudine suppresses viral replication but will not eliminate the virus. Experimentally, the drug can prevent viremia when administered (60 mg/kg per day) within 96 hours of infection. Zidovudine (30 mg/kg per day) inhibited antigenemia in kittens and prolonged survival time from 35 to 102 weeks. Myelosuppression, however, occurred in 33% of the treated cats. Zidovudine may be beneficial in reducing FeLV-associated diseases; one study reported improved health status and a reduction of oral lesions in cats with FeLV-associated stomatitis. Phosphomethoxyethyl adenine (PMEA), another reverse transcriptase inhibitor, also has been studied in cats. Cats with stomatitis associated with FeLV responded better to PMEA (AZT given at 5 mg/kg every 12 hours), but adverse reactions to the drug are likely to limit its use.

Other therapies have been studied or reported after empiric use in cats with FeLV-related diseases. Antibodies that target gp70 have proved useful experimentally only when given within 3 weeks of the initial infection. Immunostimulants (interferon-α, staphylococcal protein A, *Propionibacterium acnes,* acemannan) have been studied with variable success, but no well-designed study has proved efficacy. Of these products, interferon-α has been shown scientifically to reduce the development of disease (but not reverse viremia), thus prolonging survival. Staphylococcal protein A has reversed viremia in a few cats, but only a small number of cats have been studied. Ultimately, combinations of therapies (e.g., antiviral drugs combined with immunomodulators) may provide the most effective means of treating or controlling FeLV-related diseases.

Feline Immunodeficiency Virus

Feline immunodeficiency virus (FIV), like HIV, is caused by a lentevirus (Sellon, 1998). Like FeLV, transmission among cats occurs via saliva or blood, presumably through bite wounds. Transmission also can occur in utero or via milk in nursing infants. Viral replication begins in lymphoid tissues and salivary glands and spreads to mononuclear cells and nonlymphoid organs. Clinical signs may occur during the initial phases of viremia. The receptor for FIV is not known, but it is not CD4+. Because CD4+ cells decrease early, FIV causes progressive disruption of normal immune function. The cause of the decrease is not known, but the result is an inversion of the normal CD4+/CD8+ ratio in infected cats. CD8+ cells may increase, contributing to the inversion. Formation of immunoglobulins (dysregulation may lead to hypergammaglobulinemia in some cases) and cytokines also is disrupted. Several phases of infection have been described after infection with FIV: an acute phase, followed by a clinically asymptomatic phase that varies in duration, and a terminal phase. Other phases have been described by other investigators.

As with HIV, clinical signs of FIV are highly variable, reflecting different tissues and the role of secondary pathogens. Secondary bacterial infections reflect opportunistic microflora. Infections by fungal (e.g., *Cryptococcus*) and protozoal (e.g., *Toxoplasma*) organisms also should be anticipated. Abnormal neurologic signs are not uncommon and may reflect an inflammatory response to altered astrocyte metabolism. Changes in behavior are most commonly reported, followed by seizures, paresis, motor abnormalities, and disrupted sleep patterns. Direct damage is the most common cause of neurologic signs, although secondary infection by *Toxoplasma* or *Cryptococcus* should be considered. Abnormalities in renal function and wasting disease also may reflect either abnormal function or an inflammatory response in the respective organs. Ocular diseases include anterior uveitis (due to either FIV or opportunistic secondary organisms), glaucoma, vitreal changes, retinal degeneration, and retinal hemorrhage. Respiratory disease generally reflects secondary infection. Neoplasia is a common cause for presentation. A number of tumor types have been reported in FIV-infected cats, including lymphomas (usually B cell) and leukemias.

Diagnosis is based on clinical signs and serologic testing. Therapy focuses on supportive care. Antiviral therapy thus far has been unrewarding. Both AZT and PMEA have been studied, with neither drug preventing infection. The onset to detectable viremia and immunologic changes can, however, be prolonged. A trend toward normalization of inverted CD4+/CD8+ ratios and clinical evidence of improvement in diseases such as stomatitis have occurred. Of the two drugs, AZT is most likely to improve the quality of life of a cat infected with FIV. In general, improvements in the cat's general condition, immune status, and quality of life can be expected, along with a longer life span. Benefits of immunomodulators in cats with FIV are not clear, and assessment of scientific studies is clouded by the additional use of antibiotics and other drugs. Immunostimulation should be avoided, however, because of the association of enhanced immune response with enhanced production of FIV experimentally. Supportive therapy as described for FeLV (e.g., growth factors, antibiotics) is also appropriate for FIV.

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13 Disinfectants, Antiseptics, and Related Germicides

Harry W. Boothe

INTRODUCTION
DEFINITIONS
CHARACTERISTICS OF DISINFECTANTS AND ANTISEPTICS BY CHEMICAL TYPE
Alcohols
Aldehyde Compounds (Formaldehyde and Glutaraldehyde)
Chlorhexidine
Chlorine and Chlorine Compounds
EDTA
Ethylene Oxide
Iodine and Iodine Compounds
Peroxygen Compounds
Phenols
Quaternary Ammonium Compounds
FACTORS AFFECTING DISINFECTION AND ANTISEPSIS
DISINFECTION AND ANTISEPTIC PRACTICES
Veterinary Hospital Disinfection
Surgical Antisepsis
  Surgical Preparation of the Skin
  Surgical Preparation of Mucous Membranes
Wound Antisepsis

INTRODUCTION

Disinfectants, antiseptics, and germicides are expected to play an even more important role in the future in controlling microbes in both the veterinary patient and hospital (King, 1995). When used properly, disinfectants, antiseptics, and germicides participate in both the prevention and treatment of disease. Despite there being as many as 300 germicidal products available, just over 10 of these are in more than 90% of the registered products in the United States (Favero and Bond, 1991). The veterinary clinician needs to be familiar with only a relatively few germicidal products to make an informed decision concerning their selection and use.

Definitions of appropriate terms, characteristics of disinfectants and antiseptics by chemical type, factors affecting disinfection and antisepsis, and disinfection and antiseptic practices germane to veterinary practice are reviewed in this chapter. It is hoped that, through greater understanding of the properties of disinfectants and antiseptics, veterinary clinicians will use them appropriately.

DEFINITIONS

Pertinent to the subject of disinfection and antisepsis are the following definitions (Block, 1991a; Greene, 1998):

Sterilization: The act or process, physical or chemical, that destroys or eliminates all forms of life, especially microorganisms.

Disinfection: The killing of pathogenic agents by chemical or physical means directly applied. Disinfection processes lack the margin of safety achieved by sterilization procedures, particularly concerning their lack of sporicidal power.

Disinfectant: An agent, usually chemical, that frees from infection by destroying disease-producing or other harmful microorganisms. This term generally refers to substances applied to inanimate objects.

High-level disinfectant: An agent that has effectiveness against bacterial endospores under the proper conditions. High-level disinfectants are to be used on critical items (items that, if contaminated, impart a substantial risk of infection to the patient).

Intermediate-level disinfectant: An agent that inactivates the tubercle bacillus but does not necessarily kill bacterial spores. These disinfectants may be used on semicritical items, which carry an intermediate risk of inducing infection in the patient.

Low-level disinfectant: An agent that rapidly kills vegetative forms of bacteria and fungi but cannot be relied on to destroy, within a practical period of time, bacterial endospores, tubercle bacillus, or small nonlipid viruses. These disinfectants are indicated only for use on noncritical items that carry relatively little risk of inducing infection in the patient.

Antiseptic: A substance that prevents or arrests the growth or action of microorganisms on living tissue either by inhibiting their activity or by destroying them.

Germicide: An agent that destroys microorganisms, especially pathogenic organisms.

The distinction between disinfectants and antiseptics is not always clear (Table 13–1). Antiseptics are usually the weakest and least toxic of the surface antimicrobials (Kahrs, 1995). Antiseptics may be used on intact skin or mucous membranes before a surgical procedure or in the treatment of open wounds. Regardless of their use, antiseptics should exert a sustained effect against microorganisms without causing tissue damage (Brown and Zitelli, 1993). Although some specific germicides may be used as both disinfectants and antiseptics (e.g., alcohols and iodines), it is not generally recommended to use an antiseptic for the purpose of disinfection and vice versa.

Table 13–1. Categorization of Germicides—Disinfectants, Antiseptics, or Both

Germicides Most Appropriately Used as Disinfectants	Germicides Most Appropriately Used as Antiseptics	Germicides Effective as Both Disinfectants and Antiseptics
Aldehyde compounds (formaldehyde and glutaraldehyde)	Chlorhexidine	Alcohols
Chlorine and chlorine compounds	Dilute sodium hypochlorite solution (Dakin's solution)	Chloroxylenols
Ethylene oxide	EDTA	Iodines
Hydrogen peroxide	Iodophors	
Phenols		
Quaternary ammonium compounds		

CHARACTERISTICS OF DISINFECTANTS AND ANTISEPTICS BY CHEMICAL TYPE

The characteristics of the following 10 types of disinfectants, antiseptics, and germicides are presented: alcohols, aldehyde compounds (formaldehyde and glutaraldehyde), chlorhexidine, chlorine and chlorine compounds, ethylenediaminetetraacetate (EDTA), ethylene oxide, iodine and iodine compounds, peroxygen compounds, phenols (including chloroxylenols), and quaternary ammonium compounds. Mechanism of action (presumed or established), classification as to level of germicidal activity, commonly available preparations, efficacy, and uses are presented for each chemical type (Fig. 13–1).

Alcohols

Alcohols possess the following features desirable for a disinfectant: bactericidal action against vegetative forms, relative inexpense, ease of availability, and relative nontoxicity when used topically (Larson and Morton, 1991). Alcohols are used alone or in combination with phenols, chlorhexidine, iodines, and quaternary ammonium compounds (Jeffrey, 1995). Alcohols appear to exhibit their antimicrobial effect by denaturing proteins. Lysis of some microorganisms may occur, although the bacteriostatic action of alcohols is due to the inhibition of cell metabolites. Some water is required for alcohols to be most effective. Alcohols are considered to have intermediate-level germicidal activity. Two forms of alcohol are used most commonly: ethyl alcohol and isopropyl alcohol. Ethyl alcohol has enhanced virucidal properties and reduced toxicity compared with isopropyl alcohol, which has slightly greater bactericidal action.

Alcohols, when used alone, are more effective antiseptics than disinfectants. Alcohols are not good cleaning agents and are not recommended in the presence of physical dirt (Larson, 1995). In appropriate concentrations, alcohols provide the most rapid and greatest reduction in microbial counts on intact skin. Immersion of the hands and arms in a 65.5% solution of ethanol for 1 minute is as effective as scrubbing for 4 to 7 minutes (Larson and Morton, 1991; Larson, 1995). Alcohols should not be used in open wounds. Alcohols should be allowed to evaporate thoroughly from the skin to be fully effective and to decrease irritation (Larson, 1995). Because of their inability to destroy bacterial spores, alcohols are not recommended for disinfection of surgical instruments.

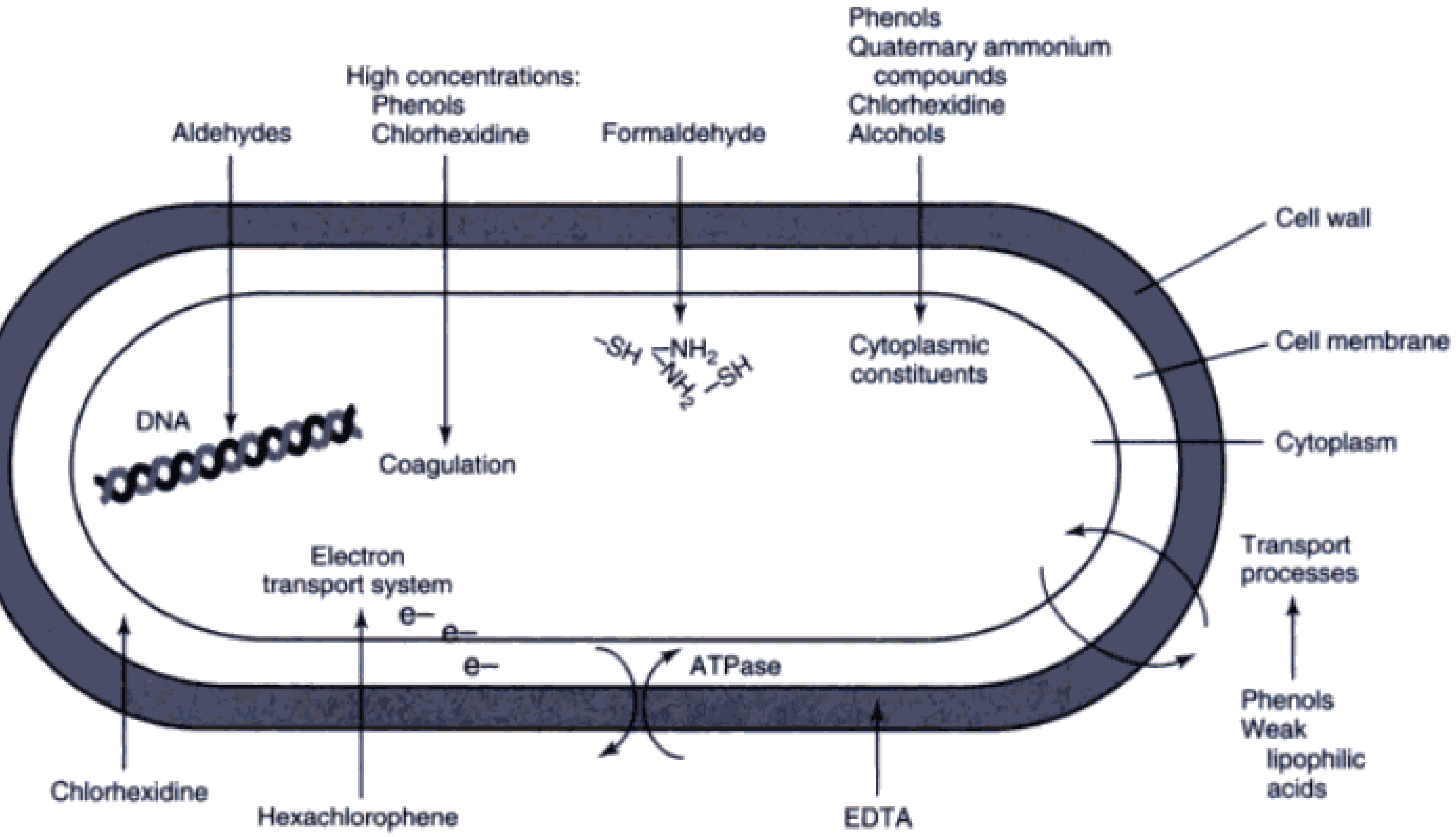

Figure 13–1. Diagram showing targets within the microbe for selected disinfectants, antiseptics, and germicides.

Aldehyde Compounds (Formaldehyde and Glutaraldehyde)

Formaldehyde (3% to 8% solutions) exhibits intermediate-level to high-level disinfection. It is sporicidal, with its mechanism of action being the ability to combine with protein, RNA, and DNA in the spore (Rossmoore, 1991). Formaldehyde does not penetrate well, and its fumes are irritating (Jeffrey, 1995). It is used infrequently as a disinfectant in veterinary hospitals.

Glutaraldehyde has been used as a "chemosterilizing" agent for about 40 years (Hugo, 1995). It displays potent bactericidal, fungicidal, virucidal, mycobactericidal, and sporicidal activity (Russell, 1994; Denyer and Stewart, 1998). Glutaraldehyde acts on proteins by denaturation and on nucleic acids by alkylation (Maris, 1995). It is classified as an intermediate-level to high-level germicide.

Factors that influence the activity of glutaraldehyde include time of contact, temperature, concentration, pH, and the presence of soiling material (Russell, 1994). Glutaraldehyde shows a very marked, temperature-dependent activity (Russell, 1994). The pH affects the stability and biocidal activity of glutaraldehyde. Glutaraldehyde is more stable at acid pH, but it is more active at alkaline pH (around 8 to 8.5). As pH increases, the number of reactive sites to which glutaraldehyde binds is increased, thus enhancing its lethal effect (Russell, 1994). At alkaline pH, glutaraldehyde penetrates more extensively into the spore, where it fixes the cortex (Scott and Gorman, 1991). The negative effect of organic matter is more apparent when lower concentrations of glutaraldehyde are used. Alkaline glutaraldehyde (2%) takes longer to be effective in the presence of organic matter (Jeffrey, 1995). Glutaraldehyde has a dual role against bacterial biofilms (a characteristic of some bacteria that make them more resistant to disinfection): an ability to penetrate the biofilm and inhibit microbial cells protected by the film and an acceleration of the detachment rate of bacteria from the biofilm (Russell, 1994).

Disinfectants containing 2% glutaraldehyde are considered high-level disinfectants with recommended contact times of 10 to 30 minutes. Exposure times of 6 to 10 hours frequently result in sterilization. Glutaraldehyde is used widely as a disinfectant for heat-labile equipment (e.g., endoscopes). Glutaraldehyde disinfectants are not as noxious, irritating to the skin, or corrosive as formaldehyde; however, precautions should be taken with their use. Gloves, safety goggles, and proper ventilation are recommended to minimize risks to those disinfecting the equipment, and glutaraldehyde-disinfected equipment should be thoroughly rinsed with sterile water before use to reduce risk to the patient (Scott and Gorman, 1991).

Chlorhexidine

Chlorhexidine is a cationic bisbiguanide, not related to hexachlorophene, that was first synthesized in 1950 (Denton, 1991). It is available as a solution and as a scrubbing agent. Chlorhexidine solution is used principally as a topical antiseptic on skin wounds and mucous membranes, but it is also used as a pharmaceutical preservative. Chlorhexidine scrub is used to preoperatively prepare the surgeon and patient. Chlorhexidine exhibits a broad spectrum of antibacterial activity, strong binding to the skin, ability to adsorb to negatively charged surfaces in the mouth (e.g., tooth and oral mucosa), persistence, low toxicity, and a minimal negative effect on activity by blood or other organic material (Larson, 1995). Chlorhexidine has its major antibacterial action by interference with the function of cellular membranes, with the primary site of action being the cytoplasmic membrane (Barrett-Bee et al., 1994; Maris, 1995; Denyer and Stewart, 1998). Rupture of the cytoplasmic membrane of the microbe occurs without lysis of the cell wall. Chlorhexidine has low-level to intermediate-level germicidal activity.

Chlorhexidine has a very rapid bactericidal effect as well as persistence of action (Maris, 1995). It has limited fungicidal and virucidal properties (Jeffrey, 1995). Chlorhexidine is more effective against gram-positive than gram-negative bacteria and exhibits a bacteriostatic effect against some bacteria (Larson, 1995; Jeffrey, 1995). The potential for the development of bacterial resistance to chlorhexidine seems low, but it has been reported (Larson, 1995; Chapman, 1998). The optimum range of pH for activity of chlorhexidine is 5.5 to 7.0. Chlorhexidine is incompatible with anionic detergents and inorganic anionic compounds (Jeffrey, 1995); thus, standing soap lather should be removed by rinsing before chlorhexidine solution is applied to the skin. Chlorhexidine forms a precipitate when diluted with electrolyte solutions, but this precipitate does not affect antimicrobial activity (Lozier et al., 1992).

Chlorhexidine is available as an alcoholic solution (scrub) that is used in the preoperative skin preparation of the surgeon and patient and as an aqueous solution. Two preparations that are used commonly in veterinary hospitals are chlorhexidine gluconate (scrub) and chlorhexidine diacetate (solution). There are few reports of adverse reactions with chlorhexidine. Chlorhexidine scrub should be used only on intact skin, never in wounds. Negligible absorption from the alimentary tract occurs, and the incidences of skin irritation and hypersensitivity are low. Chlorhexidine is ototoxic when placed in the middle ear cavity, and its use on the brain or meninges is contraindicated. In general, chlorhexidine solution (0.05%) is an effective and well-tolerated wound antiseptic in veterinary patients (Amber et al., 1983; Lozier et al., 1992).

Chlorine and Chlorine Compounds

Chlorine disinfectants are readily available, inexpensive, have a broad antimicrobial spectrum, and present minimal environmental hazards (Kahrs, 1995). Mechanism of action appears to be through oxidation of peptide links and denaturation of proteins (Maris, 1995). Intracellular accumulation results in inhibition of essential enzyme systems (Denyer and Stewart, 1998). Chlorine compounds are classified as intermediate-level disinfectants. Two factors that affect the biocidal activity of chlorine are pH and the presence of organic material. The greatest influence on the antimicrobial activity of chlorine in solution appears to be pH. With decreasing pH there is increasing biocidal activity. This increased activity at lower pH is due to a higher concentration of undissociated hypochlorous acid, which has a greater bactericidal action than the dissociated form. Organic matter consumes available chlorine and reduces its antibacterial efficacy (Dychdala, 1991). This negative effect is particularly evident in solutions with low levels of chlorine. Small additions of iodine or bromine to chlorine solutions greatly enhance their bactericidal activity.

Sodium hypochlorite appears to be the chlorine compound most frequently used as a disinfectant in veterinary hospitals. It is an effective virucidal agent (Kennedy et al., 1995). Sodium hypochlorite was first introduced as an antiseptic in 1915 as Dakin's solution (0.4% available chlorine) (Doughty, 1994). Although still used as a wound antiseptic, sodium hypochlorite is used more frequently as a disinfectant in veterinary hospitals as a 0.16% solution (1:32 dilution of 5.25% stock solution) of liquid bleach.

EDTA

EDTA, especially in combination with Tris buffer ([hydroxymethyl]aminomethane), has been shown to have antibacterial properties, particularly against certain gram-negative bacteria. Tris-EDTA acts by increasing cell wall and membrane permeability and by slowing degradation of ribosomes (Ashworth and Nelson, 1990; Denyer and Stewart, 1998). The clinical use of Tris-EDTA has been limited largely to four major pathogens: *Pseudomonas aeruginosa, Proteus vulgaris, Escherichia coli,* and *Staphylococcus aureus* (Ashworth and Nelson, 1990). Tris-EDTA decreases the minimal inhibitory concentration for these bacteria when selected antibiotics are added in vitro (Wooley and Jones, 1983). It also potentiates the antibacterial effects of chlorhexidine diacetate in lavage solutions (Klohnen et al., 1996).

Tris-EDTA solution is inexpensive and easily prepared. Ingredients include 1.2 g of EDTA and 6.05 g of Tris added to 1 L of sterile water for injection. The pH is adjusted to 8.0 by addition of acetic acid, and the solution is autoclaved. Tris-EDTA has been used as an irrigant in combination with antibiotics in the treatment of otitis externa, bacterial rhinitis, and multiple fistulas in dogs (Ashworth and Nelson, 1990). Formulations of other germicidal agents (e.g., chloroxylenol) may contain EDTA. Such preparations have enhanced efficacy against *P. aeruginosa* organisms (Stubbs et al., 1996).

Ethylene Oxide

Recognition of the biocidal activity of ethylene oxide took over 60 years after its discovery in the 1850s. Ethylene oxide was patented in the United States in 1936 for use as a gas-phase biocide (Hugo, 1995). It is a high-level disinfectant when used under proper conditions. Variables that are critical to the action of ethylene oxide include prehumidification, temperature, and concentration. Ethylene oxide sterilization is used currently for heat-labile equipment. Ethylene oxide exhibits its bactericidal and sporicidal activities because of its reaction with nucleic acids (Parisi and Young, 1991). It may be combined with either carbon dioxide or fluorocarbons. Because of its toxicity, mutagenicity, carcinogenicity, and irritation to eyes and mucous membranes, ethylene oxide sterilization for heat-labile equipment is being challenged by other safer techniques, such as plasma sterilization (see later discussion of peroxygen compounds).

Iodine and Iodine Compounds

The first reference to the use of iodine for wounds was made in 1839 (Gottardi, 1991; Hugo, 1995). Iodine is an excellent, prompt, effective microbiocide with a broad range of action. Of the seven different forms of iodine that are present in pure aqueous iodine solutions, only two play a role in the disinfection processes: molecular iodine (I_2) and hypoiodic acid (HOI). Molecular iodine has superior sporicidal and cysticidal properties compared with HOI. Iodine acts by decreasing the oxygen requirements of aerobic microorganisms (Maris, 1995). Iodine also interacts preferentially with the proteins of the cytoplasmic membrane (Maris, 1995). Although bacterial resistance to iodine seems to be uncommon, with no reports of bacterial resistance to povidone-iodine preparations as of 1993 (Goldenheim, 1993), bacterial resistance to povidone-iodine has been reported (Chapman, 1998). Iodine has comparatively low reactivity with proteins, except blood, and pH has little effect on antimicrobial efficacy. Blood reduces the efficacy of iodine by converting it into nonbactericidal iodide.

Two main groups of iodine preparations are used clinically: preparations releasing free iodine and those containing complex-bound iodine. Preparations that release free iodine have intermediate-level germicidal activity. Preparations that release free iodine include *iodine topical solution,* an aqueous solution containing 2% iodine and 2.4% sodium iodide; *strong iodine solution (Lugol's solution),* an aqueous solution containing 5% iodine and 10% potassium iodide; *iodine tincture,* containing 2% iodine and 2.4% sodium iodide in aqueous ethanol (1:1); and *strong iodine tincture,* containing 7% iodine and 5% potassium iodide in 95% ethanol. Iodine tincture preparations are both more efficacious and more toxic than aqueous solutions, including iodophors.

Preparations containing complex-bound iodine have low-level to intermediate-level activity. Iodophors are the most commonly used preparations that contain complex-bound iodine. The iodine in iodophors is bound to a carrier of high molecular weight (e.g., polyvinyl pyrrolidone). Such carriers tend to increase the solubility of iodine, provide a sustained-release reservoir, reduce the equilibrium concentration of free molecular iodine, improve the wetting properties of the iodine, and aid in penetration of iodine in organic soil, including fat (Gottardi, 1991).

The best known iodophor is povidone-iodine. Povidone-iodine compounds have a pH of about 5. The bactericidal properties of iodophors depend on the liberation of free iodine (LeVeen et al., 1993). The amount of free iodine in iodophor preparations depends on concentration, being greatest in a 0.07% solution of povidone-iodine (Lemarié and Hosgood, 1995). Although in vitro studies have shown povidone-iodine to be highly effective against selective bacteria, including methicillin-resistant *S. aureus* (Goldenheim, 1993), in vivo studies provide conflicting data regarding efficacy (Doughty, 1994). LeVeen et al. (1993)

conclude that, based on clinical and experimental evidence, free iodine is not liberated from povidone-iodine in therapeutic concentrations. Clinical studies indicate that povidone-iodine is suitable as an antiseptic on intact skin (LeVeen et al., 1993).

Iodine-containing preparations, particularly iodophors, are used frequently as antiseptics. Iodophors are available in a variety of forms, including 10% solution, 2% cleansing solution (scrub), and 2% aerosol spray. Presurgical skin disinfection of surgeon and patient, disinfection of mucous membranes, and wound disinfection are the most common uses of iodophors. Povidone-iodine also has been reviewed favorably as an oral antiseptic (Rahn, 1993). Cutaneous absorption of iodine, particularly in traumatized skin, can lead to increased serum iodine levels. Systemic iodine toxicity is also possible when iodophors are used to treat large, open wounds (Doughty, 1994). Also, iodophors produce adverse effects when placed in the peritoneal cavity; hence, their use in the peritoneal cavity is not recommended.

Peroxygen Compounds

Hydrogen peroxide has historical and current application as a disinfectant and antiseptic. As a 3% solution, hydrogen peroxide has limited bactericidal effectiveness and is usually classified as an intermediate-level germicide (Doughty, 1994). It acts by denaturing proteins and lipids of microorganisms (Maris, 1995). Hydrogen peroxide (3%) provides an effervescent cleansing action; however, because of its cytotoxicity, hydrogen peroxide is inappropriate as an antiseptic (Doughty, 1994; Greene, 1998). As a 58% solution, however, and in the presence of an electromagnetic field, hydrogen peroxide becomes a gas plasma. As a gas plasma, hydrogen peroxide destroys microorganisms and is classified as a high-level disinfectant. Hydrogen peroxide (58% solution) is sporicidal by virtue of its effect on the outer spore layers and the spore core (Block, 1991b). Because the process temperature associated with plasma sterilization does not exceed 40°C, plasma sterilization is particularly well suited to materials that cannot be steam sterilized. Because of its relative safety, plasma sterilization is emerging as an alternative to ethylene oxide gas in the sterilization of heat-labile articles. Other peroxygen compounds, such as peracetic acid and ozone, have little use as veterinary disinfectants.

Phenols

Carbolic acid, a phenol, is the oldest example of an antiseptic compound (Heit and Riviere, 1995). Phenols have a wide spectrum of activity against bacteria, viruses, and fungi, but they have minimal sporicidal activity (Jeffrey, 1995). They act on the cytoplasmic membrane, producing leakage and disrupting membrane transport (Denyer and Stewart, 1998). Phenols are classified as low-level to intermediate-level germicides. Phenols no longer play a significant role as antibacterial agents, in part because of their toxicity (O'Connor and Rubino, 1991).

Hexachlorophene, a chlorinated phenol derivative, was used as a presurgical antiseptic primarily by surgeons, but its toxicity has limited its use (Terleckyj et al., 1995). The chloroxylenols, synthetic halogen-substituted phenol derivatives, have been used extensively as preservatives, disinfectants, and topical antiseptics (Stubbs et al., 1996).

Quaternary Ammonium Compounds

Introduced in 1916, quaternary ammonium compounds are surface-active cations that exhibit low-level germicidal activity (Hugo, 1995). They bind irreversibly to the phospholipids and proteins of the cytoplasmic membrane of microbes, impairing permeability (Maris, 1995; Denyer and Stewart, 1998). Quaternary ammonium compounds are much more effective in preventing the growth of bacteria than in killing them, and they are far more effective against gram-positive than gram-negative bacteria (Jeffrey, 1995). They possess a narrow margin of safety and can fail when exposed to resistant microorganisms (Terleckyj et al., 1995).

Quaternary ammonium compounds with a carbon chain length of 14 demonstrate the highest level of bactericidal activity (Merianos, 1991). They were used initially as an adjunct to surgery, such as in presurgical patient preparation, but this use has been curtailed, in part because of the observation that skin bacteria survive beneath the layer of applied quaternary ammonium compound. Additionally, quaternary ammonium compounds tend to be inactivated by lipids in organic matter, and their activity is adversely affected by soap, hard water, and gauze (Terleckyj et al., 1995). Quaternary ammonium compounds are currently used primarily for environmental disinfection of floors, walls, and equipment surfaces. Benzalkonium chloride is used as a topical antifungal agent for horses at a concentration of 0.15%.

FACTORS AFFECTING DISINFECTION AND ANTISEPSIS

A successful disinfection plan requires initial consideration of microbial susceptibility and environmental conditions (Grow, 1995). Factors of importance when selecting a chemical germicide include the degree of microbial killing required; the nature and composition of the surface item or device to be treated; amount of organic matter present, number and resistance of microorganisms present; presence of microbial biofilms; and cost, safety, and ease of use of the available agents (Favero and Bond, 1991). Critical items, which, if contaminated, impart a substantial risk of infection, must be sterilized. Noncritical items, which only touch intact skin of the patient during routine use, can be disinfected. The greater the risk of infection associated with the use of a device, the more complete must be the degree of microbial killing on that device. The nature and composition of the device or surface to be treated impact the ease with which that device may be disinfected. Smooth, nonporous, and cleanable surfaces (e.g., table surfaces) are easiest to disinfect, whereas crevices, joints, and pores (e.g., surgical clamps) constitute barriers to the penetration of liquid germicides (Favero and Bond, 1991).

The amount of organic material present has a major impact on efficacy of most disinfectants. Physical cleaning before disinfection is often the most important step in the disinfection process (Favero and Bond, 1991). Endoscopes are particularly challenging to clean properly. Organic material has an especially profound effect on the germicidal efficacy of chlorine-based and iodine-based disinfectants and quaternary ammonium compounds (Favero and Bond, 1991). Negative effects of organic material are particularly profound with weak concentrations and with low-level disinfectants.

The number and resistance of microorganisms present can influence germicidal efficacy. In general, the higher the level of microbial contamination, the longer must be the exposure to the chemical germicide before the entire microbial population is killed (Favero and Bond, 1991). Microorganisms vary widely in their resistance to chemical germicides, with bacterial spores being most resistant, then protozoal cysts, coccidial oocysts, tubercle bacilli, small nonlipid viruses, fungi, vegetative bacteria, and medium-sized lipid viruses (Greene, 1998). Differences in resistance exhibited by various vegetative bacteria are relatively minor, with staphylococci and enterococci being the more resistant gram-positive bacteria and *Pseudomonas, Klebsiella, Enterobacter,* and *Serratia* species showing greater resistance than other gram-negative bacteria (Favero and Bond, 1991). The resistance of some bacteria, such as *Pseudomonas* species may relate, in part, to the production of a glycocalyx-based biofilm (Terleckyj et al., 1995; Russell, 1995).

Some bacteria (e.g., *Escherichia coli, Pseudomonas* species) produce biofilms (Terleckyj et al., 1995; Ntsama-Essomba et al., 1997). Biofilms are a glycocalyx-based capsule produced by bacteria in natural aquatic environments (Terleckyj et al., 1995). They surround bacteria and make them more resistant to disinfection. Biofilms may be encountered in medical implants, such as catheters, drain tubes, sutures, and prosthetic hip joints, and seem to present a barrier to penetration by disinfectants (Terleckyj et al., 1995; Russell, 1995). The reduced accessibility of the bacteria included in the biofilm appears to be the major factor in resistance development (Ntsama-Essomba et al., 1997). Resistance depends on the nature of the disinfectant, with greater resistance reported with selected quaternary ammonium compounds (e.g., benzalkonium chloride) and less resistance with oxidizing agents (e.g., sodium hypochlorite and hydrogen peroxide) and phenolic derivatives (Ntsama-Essomba et al., 1997).

Cost may be a factor in selection of disinfectants and antiseptics. One of the major impacts on cost of a disinfection procedure is the dilution of germicide used. Although overdilution of a germicide will reduce its net cost, overdilution may also significantly reduce its germicidal potency. Recommendations of the manufacturer should be followed when diluting a germicide. Selection of germicides should be based primarily on efficacy and safety, not cost. Ease of use of a germicide can affect disinfection practices. Those agents with wider safety margins are likely to be easier to use.

Other causes of disinfection failure include poor disinfectant penetration or coverage, insufficient contact time, and inadequate temperature and humidity while the disinfectant is being applied (Kahrs, 1995; Russell, 1995). Natural and acquired resistances to disinfectants have been observed (Kahrs, 1995; Russell, 1995); however, some agents, such as povidone-iodine, have not had resistance documented (Goldenheim, 1993).

DISINFECTION AND ANTISEPTIC PRACTICES

Veterinary Hospital Disinfection

The two types of disinfection practices in a veterinary hospital are immersion disinfection and surface disinfection, including cabinets, tables (examination, treatment, and surgery), kennels, lights, and chairs (Heit and Riviere, 1995). Agents that have been used for immersion disinfection include 2% alkaline glutaraldehyde, isopropyl alcohol (thermometers), chlorhexidine diacetate, and quaternary ammonium compounds. Of these agents, only 2% alkaline glutaraldehyde is reliable. Because the disinfection of surgical instruments by immersion lacks the safety of heat-pressure sterilization, immersion disinfection is not recommended for instruments to be used during aseptic surgery.

Surface disinfection in a veterinary hospital can be particularly important in minimizing spread of disease. Thorough cleaning of the surface before disinfection is a critical step. Other factors that improve the efficacy of surface disinfection include adequately covering the surface with the disinfectant and maintaining contact for a sufficient time. Agents that are used as surface disinfectants include sodium hypochlorite and quaternary ammonium compounds. Sodium hypochlorite is used as a 0.16% solution (1:32 dilution of 5.25% solution) of liquid bleach to disinfect kennels and tables. Such a solution has been shown to be effective in neutralizing parvovirus (McGavin, 1987). Quaternary ammonium compounds are surfactants that have both cleansing and disinfecting properties. Despite their cleansing properties, quaternary ammonium compounds have reduced germicidal efficacy in the presence of organic material; hence, cleaning of surfaces before their use is indicated. Quaternary ammonium compounds have been recommended for the routine disinfection of environmental surfaces (Terleckyj et al., 1995).

Surgical Antisepsis

Surgical antisepsis is the application of antimicrobial chemicals to skin, mucosa, and wounds to reduce the risk of infection (Gröeschel and Pruett, 1991). Surgical antisepsis most commonly involves the removal or reduction of normal flora by the topical application of antimicrobial substances to the intact skin before a surgical procedure. Distinguishing between antiseptic use on intact skin and that on mucous membranes or in wounds is important. Different formulations and concentrations of antiseptics are indicated depending on their use. Preparations containing alcohol or detergents (scrubs) are only to be used on intact skin. The concentration of antiseptic used for wounds is less, in general, than that applied to intact skin.

Surgical Preparation of the Skin

The purpose of a surgical hand scrub is to remove transient flora and reduce resident flora for the duration of surgery in case of glove tears (Larson, 1995). Regardless of the antimicrobial agent used, the technique of hand washing is important. The primary problem with hand hygiene is not a paucity of good products, but rather the laxity of practice (Larson, 1995). Nails should be short, and artificial nails and nail polish should be avoided (Larson, 1995). Debris should be removed from under the fingernails with a nail cleaner after the hands and forearms have been washed thoroughly. The subungual area has higher microbial counts, and contamination of the hands can increase when gloves create a warm, moist environment (Larson, 1995). Duration of washing is important both for mechanical action and to allow antimicrobial products sufficient contact time to achieve the desired effect (Larson, 1995). Although the American College of Surgeons suggests that a surgical scrub of 120 seconds, including brushing of the nail and fingertip areas, is adequate (Larson, 1995), a 6-minute scrub is often used by veterinary surgeons.

Selection of an appropriate antimicrobial agent for surgical hand scrubbing should be made in three stages: One should determine what characteristics are desired, review and evaluate the evidence of safety and efficacy in reducing microbial counts, and consider the personnel acceptance of the product and the costs (Larson, 1995). Antiseptic treatment of the skin should not be toxic, not cause skin reactions, and not interfere with the normal protective function of the skin (Gröeschel and Pruett, 1991). Antiseptic agents used to prepare the skin of the surgeon or patient include alcohols, chlorhexidine gluconate, iodophors, and chloroxylenols.

Alcohols, in appropriate concentrations (60% to 90%), provide the most rapid and greatest reduction in microbial counts on skin (Larson, 1995). Alcohols are not good cleansing agents, and they are not recommended in the presence of physical dirt. They should be allowed to evaporate thoroughly from the skin to be fully effective and to decrease irritation (Larson, 1995). Immersion of the hands and arms of the surgeon in alcohol has been shown to be an effective technique (Larson, 1995). Alcohol is also used on the intact skin of the veterinary patient before surgery as an antiseptic (Fries, 1993).

Chlorhexidine gluconate has both rapid and persistent antibacterial activity when used as a presurgical scrub. Its persistence is probably the best of any agent currently available for hand washing (Larson, 1995). The activity of chlorhexidine is not significantly affected by blood or other organic material (Larson, 1995). The incidence of skin irritation to chlorhexidine scrub seems low, as does the potential for development of bacterial resistance. Chlorhexidine scrub may be the ideal agent for surgical preparation of the skin (Lemarié and Hosgood, 1995). Both 2% and 4% formulations in a detergent base are readily available.

Iodophors, particularly povidone-iodine, are used frequently in the presurgical preparation of surgeons and veterinary patients. The antimicrobial effects of iodophors are similar to those of iodine. Recommended levels of free iodine for antiseptics are 1 to 2 mg/L (Larson, 1995). Povidone-iodine scrub has been found to be equally effective as chlorhexidine gluconate scrub in reducing the number of bacteria on canine skin for up to 1 hour after application (Osuna et al., 1990). Iodophors are rapidly neutralized in the presence of organic materials such as blood (Larson, 1995). They have a propensity toward skin irritation, and cutaneous absorption can cause thyroid dysfunction. Iodophors are available as a surgical scrub (2%) and as a solution (10% and 2%).

Chloroxylenols are synthetic phenol derivatives that have been used sparingly as a presurgical scrub of surgeons and veterinary patients. They are less effective than either chlorhexidine or iodophors in reducing skin flora, but chloroxylenols may have a lower incidence of skin irritation than iodophors (Larson, 1995). Their activity is only minimally affected by organic matter (Larson, 1995). Two formulations may be used as a presurgical scrub: 3% chloroxylenol and 1.5% para-chloro-meta-xylenol.

Surgical Preparation of Mucous Membranes

Antisepsis of mucous membranes, particularly the oral mucosa, present particular problems. The bacterial colonization of the oral cavity is very high, and the efficacy of oral antiseptics is affected by dilution effects as well as inactivation due to salivary proteins (Rahn, 1993). Also, an increase in antiseptic concentration is limited by local irritation and a high absorption rate with the risk of systemic intoxication (Rahn, 1993). Only a few solutions are useful as oral antiseptics: povidone-iodine, chlorhexidine, and hexetidine (Rahn, 1993). Povidone-iodine solution has been shown to reduce inflammation and the progression of periodontal disease as well as bacteremia after dental extractions (Rahn, 1993).

Chlorhexidine solution is an effective agent for the prevention and treatment of oral disease (Denton, 1991). Its effectiveness stems from its ability to adsorb to negatively charged surfaces in the mouth, such as the tooth and mucosa. Hexetidine is used as a 0.1% solution for local infections and oral hygiene. It has been shown to have similar antimicrobial efficacy against common buccal organisms as 0.2% chlorhexidine (Ashley, 1984).

Wound Antisepsis

When topically treating a contaminated wound with an antiseptic solution, one should choose an appropriate type and concentration of antiseptic that has both antibacterial properties and minimal negative effects on wound healing. Antiseptics that appear to fulfill these criteria include povidone-iodine solution, chlorhexidine diacetate solution, and sodium hypochlorite solution (Dakin's solution). Povidone-iodine solution appears to be most effective and least tissue toxic in concentrations of 0.1% to 1% (Lemarié and Hosgood, 1995). Povidone-iodine concentrations greater than 0.5% are cytotoxic to the canine fibroblast in vitro (Lemarié and Hosgood, 1995). Povidone-iodine should be used judiciously on large wounds because of the potential for systemic absorption of iodine.

Chlorhexidine diacetate solution (0.05%) has a wide spectrum of antimicrobial activity as well as minimal deleterious effects on wound healing (Swaim and Lee, 1987).

Its sustained residual activity seems to be an advantage in wound therapy. Dilution of the stock solution with sterile water, 0.9% sodium chloride, or lactated Ringer's solution does not adversely affect its antibacterial activity (Lozier et al., 1992).

A dilute Dakin's solution (0.005% sodium hypochlorite) has been shown to be both bactericidal and not damaging to fibroblasts (Swaim and Lee, 1987). Dakin's solution has been used as an effective irrigant for human wounds since World War I, and its use has persisted to the present. In vivo studies on the efficacy of Dakin's solution in canine wounds are not available (Lemarié and Hosgood, 1995).

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14 Drugs for the Treatment of Protozoal Infections

Randy C. Lynn

INTRODUCTION
COMMON ENTERIC COCCIDIOSIS
Biology
Treatment
  Sulfas and Potentiated Sulfas
  Amprolium
  Furazolidone
  Quinacrine
TOXOPLASMOSIS
Biology
  Enteroepithelial Life Cycle
  Extraintestinal Life Cycle
  Congenital Transmission
  Clinical Signs
  Diagnosis
Treatment
  Clindamycin
  Sulfa Plus Pyrimethamine
  Monensin
GIARDIA
Biology
Treatment
  Albendazole
  Fenbendazole
  Furazolidone
  Metronidazole
  Quinacrine
SUMMARY

INTRODUCTION

Protozoal infections can provide diagnostic as well as therapeutic challenges for the small animal clinician. The situations can range from the simple treatment of a young kitten with coccidiosis to the more robust challenges of chronic giardiasis in a breeding kennel. Although several of the protozoa are well characterized and relatively easy to treat, others are poorly understood and have no specific agents available for therapy. Three types of infections caused by major pathogens are presented here: common enteric coccidia, toxoplasmosis, and giardia. The pathogens are known to affect dogs and cats, and two are significant zoonotic agents.

This chapter does not include the protozoa that only appear sporadically in the veterinary literature (*Balantidium, Pentatrichomonas, Entamoeba, Hammondia, Besnoitia,* and *Sarcocystis*). These organisms are not adequately documented as pathogens of dogs and cats and thus require no therapy. Also excluded are those protozoal pathogens that are partially characterized but have no effective treatment available (*Cryptosporidium, Hepatozoon, Babesia, Cytauxzoon, Leishmania, Encephalitozoon,* and *Acanthamoeba*). Textbooks of parasitology or infectious disease should be consulted for a complete discussion of these sporadic, spurious, or untreatable pathogens (Bowman, 1999; Greene, 1998).

Therapy of protozoal infections, which are often zoonotic, must include use of therapeutic agents along with supportive therapy and proper hygiene and husbandry to clean up the environment and prevent spread to other animals and people. No therapeutic agent, no matter how safe or effective, can be expected to treat these diseases without supportive therapy and hygiene. Table 14–1 lists the therapeutic agents discussed in the text.

COMMON ENTERIC COCCIDIOSIS

Biology

The most common protozoa in small animal veterinary medicine are the coccidians, which cause a condition termed *coccidiosis.* Coccidia are very host specific. Dogs and cats are infected with several species in the genus *Isospora.* Diagnosis is readily made by conventional fecal floatation techniques using concentrated sugar or salt solutions. Careful identification of coccidia oocysts may reveal the presence of spurious coccidia from other genera, especially *Eimeria* species, which commonly parasitize food animals, thus indicating coprophagy. Nevertheless, coccidia

Table 14–1. Antiprotozoal Medications*

		Canine and Feline Protozoa	
	Coccidia	***Toxoplasma***	***Giardia***
Sulfonamides			
Sulfadimethoxine	+		
Sulfadimethoxine plus ormetoprim	+		
Sulfadiazine plus trimethoprim	+		
Sulfamethoxazole plus trimethoprim	+		
Amprolium	+		
Furazolidone	+		+
Clindamycin		+	
Sulfa plus pyrimethamine		+	
Monensin		+	
Metronidazole			+
Albendazole			+
Fenbendazole			+

*Some activities listed are not approved or require higher than approved doses.

are ubiquitous in young dogs and cats and commonly cause disease, especially in those with suboptimal nutrition, immune status, or stress.

Coccidia are obligate intracellular parasites that depend on dispersion of fecal oocysts for transmission. This fact alone illustrates the importance of hygiene. There are four species that infect dogs (*Isospora canis, I. ohioensis, I. burrowsi,* and *I. neorivolta*) and two that infect cats (*Isospora felis* and *I. rivolta*). Although direct ingestion of the oocyst is the primary means of infection, rodents can serve as paratenic hosts if they ingest the oocyst and then are eaten by the definitive host.

Coccidia have life cycles that are more complex than other infectious agents (Fig. 14–1). Each life cycle includes both sexual and asexual phases. This is important to remember because the therapeutic agents used to treat and control coccidia are primarily effective against the asexual (schizont) stage of the life cycle.

The oocyst is passed in the feces, and, after suitable exposure to air, heat, and moisture, the oocyst sporulates. This process may take only a few hours or a few days, depending on the species of coccidia and on the environmental conditions. During sporulation each oocyst develops into two sporocysts that contain four sporozoites each; thus each oocyst contains a total of eight infective sporozoites.

After ingestion, the sporozoites are liberated from the oocyst and invade the enterocytes that line the small intestine. Once inside the enterocytes, the sporozoites turn into trophozoites, which undergo asexual fission (properly termed *schizogony* or *merogony*) to produce many daughter schizonts. After 4 days the enterocyte ruptures and releases the multiple schizonts (or meronts). This schizont stage is the place in the life cycle where therapeutic agents have a chance to break the life cycle. Because the schizonts are only released from the cell every 4 days, the therapeutic agent should be present in the gut for several multiples of this period, usually 14 to 21 days. The daughter schizonts are capable of infecting new enterocytes and repeating the cycle of fission into many daughters and rupture of the subsequent enterocytes. The number of asexual cycles has been determined for each species of coccidia; the small animal pathogens typically have two or three asexual cycles before entering the sexual stage of the life cycle.

The schizont, produced by the last cycle of asexual fission, enters another enterocyte and develops into either a male or a female gametocyte. The female gametocyte enlarges and forms a singular large cellular structure within the enterocyte. The male gametocyte undergoes fission to produce many small biflagellate male sex cells. The enterocytes rupture, and the motile male sex cells fertilize the female gametocytes, which mature to a zygote and then pass out in the feces in the form of an oocyst. The fresh oocysts are exposed to the external environment where they sporulate and infect new hosts.

The repeated intracellular invasion of enterocytes and subsequent rupture can produce substantial pathology to the gut, especially if the infected host is young, weak, malnourished, or stressed. Normal animals, in otherwise good health, usually experience coccidial infection followed by an effective immune response that limits and eliminates the infection without therapeutic intervention. Most clinicians prefer to intervene when coccidia are identified in a fecal floatation. Therapy is usually successful in eliminating the coccidial oocysts, although it is not known how many of these animals would have spontaneously cleared the infection without intervention.

Treatment

Sulfas and Potentiated Sulfas

Sulfonamides are the treatments of choice for small animal coccidia. Unfortunately there is a paucity of research infor-

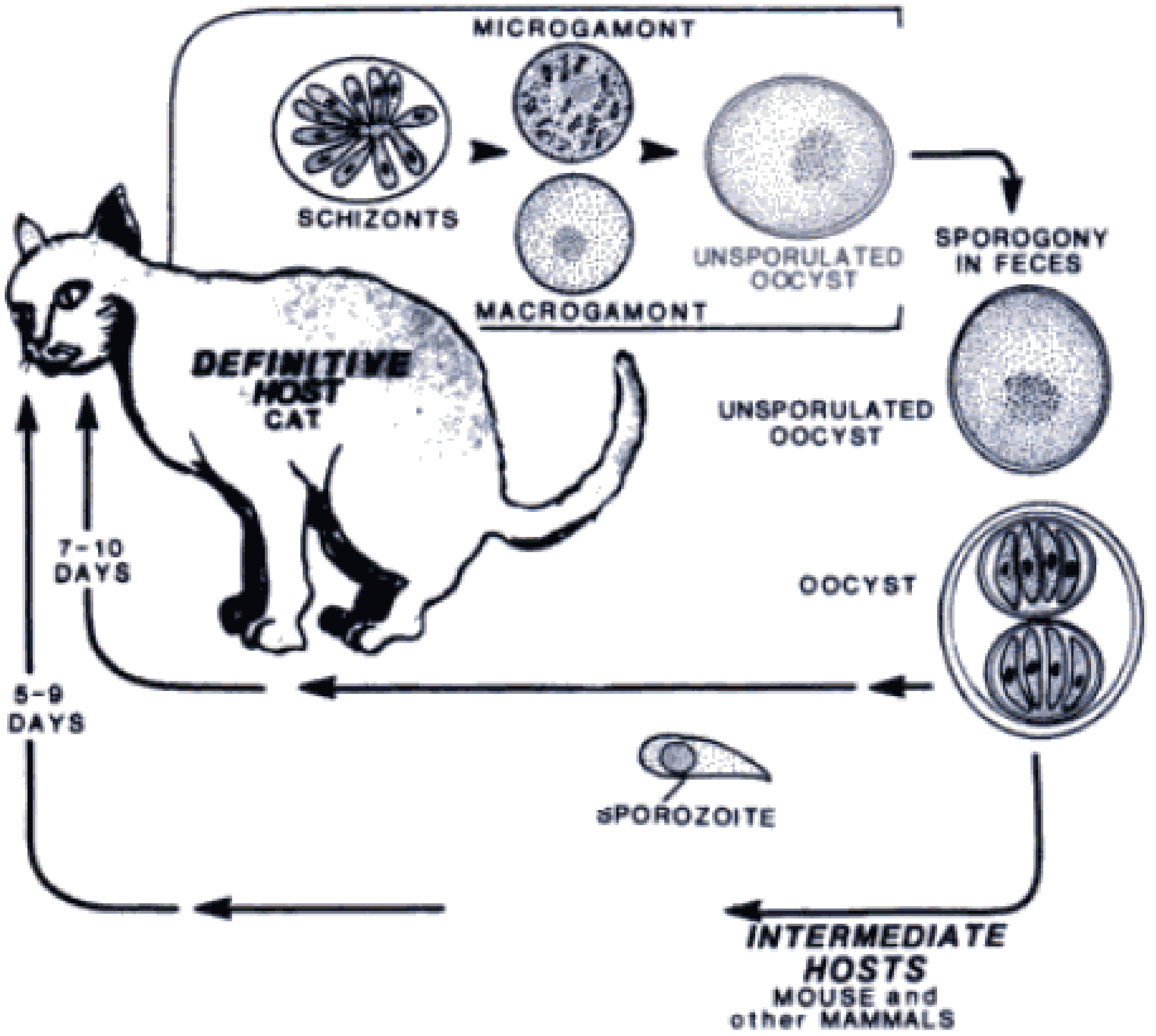

Figure 14–1. Life cycle of *Isospora felis,* which is typical of the *Isospora* spp. The mode of transmission may be direct, via ingestion of sporulated oocysts from the environment, or indirect, via ingestion of cysts in prey animals. Sexual and asexual reproduction of the parasite occurs in the intestines of the definitive host (in this case, a cat), and unsporulated oocysts are shed in the feces of definitive hosts. (From Dubey JP, Greene CE: Enteric coccidiosis. In Greene CE [ed]: Infectious Diseases of the Dog and Cat [2nd ed], p 511. Philadelphia, WB Saunders, 1998.)

mation to support their efficacy. Two pivotal studies utilizing sulfamethoxine and sulfaguanidine against coccidia support their utility; however, these two agents are no longer available in the United States (Boch et al., 1981, Correa et al., 1983). Clinicians have empirically substituted more readily available sulfonamides and enjoyed apparent clinical success (Dubey, 1993). Currently there is one simple sulfa and three potentiated sulfas that are commonly used in the United States: sulfadimethoxine (Albon), sulfadimethoxine with ormetoprim (Primor), sulfadiazine with trimethoprim (Di-Trim, Tribrissen), and sulfamethoxazole with trimethoprim (Bactrim, Septra).

Sulfonamide Chemistry and Mechanism of Action

The sulfonamides are structural analogues of para-aminobenzoic acid that competitively inhibit the dihydropterate synthetase step in the synthesis of folic acid, which is required for synthesis of RNA and DNA. Inhibition by sulfas impairs protein synthesis, metabolism, and growth of the pathogen. A vast array of sulfa agents have been created and described; all but a few have been lost in the sands of time. The important differences between these agents is their solubility, duration of action, and activity against key pathogens. Fortunately, the three sulfas included in this discussion demonstrate acceptable performance in all three categories; solubility is adequate, they are given once or twice daily, and they have a reasonably broad-spectrum of action. The sulfa drugs are primarily effective against the schizont stages of the coccidia; thus prolonged treatment may be required for the drug to effectively block the life cycle.

Potentiator Chemistry and Mechanism of Action

The diaminopyrimidine potentiators (trimethoprim and ormetoprim) act in concert with sulfonamides by blocking the next step (dihydrofolate reductase) in folic acid synthesis. Chemically the diaminopyrimidines are related to pyrimethamine, which has antimalarial properties. The agents are highly selective inhibitors of dihydrofolate reductase. This sequential blockade produces significant potentiation of activity. It is a classic case of drug potentiation.

Drug Disposition

The sulfonamides are weak acids that are well absorbed from the gastrointestinal tract and are widely distributed in the body. Sulfadimethoxine and sulfamethoxazole have high serum protein binding, which provides decreased body clearance and long half-lives. They undergo metabolic alteration in the liver and subsequent renal clearance. Trimethoprim and ormetoprim are also well absorbed from the gut, widely distributed, and then hydroxylated and excreted through the urinary tract.

Toxicity and Adverse Effects

The long history of sulfa use in veterinary medicine has resulted in a wide array of toxic and idiosyncratic reactions in animals. Historically, the most common and most avoidable reactions result from crystallization in the urinary tract with secondary crystalluria, hematuria, and urinary obstruction. Recent reviews in human medicine indicate that the improved solubility of the modern preparations has decreased the risk of crystalluria; nevertheless, it is still prudent to ensure adequate water intake and proper hydration during sulfa therapy (Cribb et al., 1996). The human literature also suggests that the sulfonamides may be directly nephrotoxic (Cribb et al., 1996). Hematopoietic disorders (thrombocytopenia and leukopenia) have also been reported as a result of sulfa therapy. Sulfaquinoxaline especially has been associated with hypothrombinemia, hemorrhage, and death in puppies receiving therapy for coccidia (Patterson and Grenn, 1975).

Idiosyncratic reactions in animals and people often include immune-mediated phenomena including hypersensitivity reactions, drug fever, urticaria, nonseptic polyarthritis, focal retinitis, and hepatitis. Fortunately, these reactions occur at very low rates when the drugs are used at recommended dose rates and for less than 2 weeks.

Preparations

There are four sulfa products that are currently available for use in small animal medicine; sulfadimethoxine, sulfadimethoxine with ormetoprim, sulfadiazine with trimethoprim, and sulfamethoxazole with trimethoprim. Each is available in a variety of formulations.

Sulfadimethoxine Sulfadimethoxine is a rapidly absorbed, long-acting sulfonamide. It is not acetylated in the dog and is excreted unchanged in the urine. It is approved for treatment of coccidiosis in dogs and cats. It has a wide margin of safety; dogs given multiple oral doses of 160 mg/kg by mouth daily for 13 weeks showed no signs of toxicity (Entriken et al., 1998).

It is important that all treated animals receive adequate water intake to prevent dehydration and crystalluria, as well as proper nutrition, during therapy for coccidiosis. Therapy is available as a 40% injection (Albon); in 125-, 250-, and 500-mg tablets (Albon); as a pleasant tasting 5% suspension (Albon); and as a 12.5% oral solution (Albon, Di-Methox). The approved therapy is an initial dose of 55 mg/kg, orally or by subcutaneous or intravenous injection, for the first day and subsequent doses of 27.5 mg/kg orally once per day for 12 to 21 days. It seems reasonable that, because coccidia are enteric pathogens, the oral route would be most effective.

Sulfadimethoxine with Ormetoprim Sulfadimethoxine with ormetoprim is the most recently approved potentiated sulfonamide. It constitutes a rational combination that potentiates the action of both drugs by blocking two sequential steps in the synthesis of folic acid. Ormetoprim is a diaminopyrimidine potentiator with very low mammalian toxicity. The available tablets contain 100/20, 200/40, 500/100, or 1000/200 mg sulfadimethoxine/mg ormetoprim, respectively (Primor). The tablets are designated by the total weight of active ingredient in each tablet; thus the "Primor 120" contains 100 mg of sulfadimethoxine and 20 mg of ormetoprim. The approved starting dose is 55 mg/kg orally on the first day of treatment and then 27.5

mg/kg orally once per day for 14 to 21 days. Do not treat beyond 21 days (Entriken et al., 1998).

It is interesting to note that the only recent controlled study of coccidiosis therapy for dogs was conducted with this drug combination. In that study, 32.5 mg/kg or 66 mg/kg was given continuously in the food for 23 days, subsequent to experimental oocyst infection. The higher dose of 66 mg/kg provided better results and did not produce any adverse reactions (Dunbar and Foreyt, 1985).

Sulfadiazine with Trimethoprim Sulfadiazine with trimethoprim is the potentiated sulfa with the most years of actual use in veterinary medicine. For many years it was the only potentiated sulfa approved for use in animals. Trimethoprim is a diaminopyrimidine potentiator with very low mammalian toxicity. The available tablets contain 25/5, 100/20, 400/80, or 800/160 mg sulfadiazine/mg trimethoprim respectively (Tribrissen, Di-Trim). The tablets are designated by the total weight of active ingredient in each tablet; thus "Tribrissen 30" contains 25 mg of sulfadiazine and 5 mg of trimethoprim. The approved dose is 30 mg/kg orally or 26.4 mg/kg by subcutaneous injection per day up to 14 days. The preferred dose for bacterial infections in dogs and cats is 30 mg/kg once or twice daily and may be indicated for severe coccidial infections. The manufacturer recommends that animals with marked hepatic parenchymal damage, blood dyscrasias, or previous sulfonamide sensitivity should not be given this product (Entriken et al., 1998; Plumb, 1999).

Sulfamethoxazole with Trimethoprim Sulfamethoxazole with trimethoprim is a readily available product approved for use in people (Bactrim, Septra); it is not currently approved for use in animals. Because of its similarity to veterinary potentiated sulfonamides and because low-cost generics are available, it is widely used in veterinary medicine. There is some controversy regarding the appropriate dosing regimen for this human-labeled product in animals, but many clinicians gain acceptable clinical results using the same dose as sulfadiazine.

Sulfamethoxazole with trimethoprim is available in a fixed combination of 5:1 sulfamethoxazole to trimethoprim as tablets and pediatric suspension. The available "single-strength" tablets contain 400/80 and "double-strength" tablets contain 800/160 mg trimethoprim, respectively (Bactrim, Septra). The pediatric oral suspension contains 40 mg sulfamethoxazole and 8 mg trimethoprim per milliliter. The dose for bacterial infections and coccidiosis in dogs and cats is 30 mg/kg once daily for 10 days (Plumb, 1999) and may be indicated in severe coccidial infections.

Amprolium

Amprolium (Amprol, Corid) is an antiprotozoal drug that is a structural analogue of thiamine. It is freely soluble in water, methanol, and ethanol. The close structural similarity between amprolium and thiamine allows amprolium to compete with thiamine for absorption into the parasite. It is most effective against the first-generation schizont stage and thus is more effective as a preventative than as a treatment.

At very high doses amprolium may produce thiamine deficiency in the host. Thiamine deficiency can be treated by adding thiamine to the diet, although excessive thiamine supplementation may decrease the efficacy against the pathogen. In dogs, adverse reactions are apparently rare and may consist of neurologic abnormalities, depression, anorexia, and diarrhea (Plumb, 1999).

Amprolium is approved for use in the drinking water or feed of poultry and cattle for the prevention and treatment of coccidia. Treatment for dogs and cats requires adapting the approved formulations to small animal use. The target dose for treatment of dogs is 100 to 200 mg/kg by mouth daily in food or water (Plumb, 1999). Dogs may be treated by mixing 30 mL (2 Tbs) of 9.6% amprolium solution to one U.S. gallon (3.8 L) of drinking water and offering it as the sole source of drinking water (Smart, 1971). Alternatively, 1.25 g of 20% amprolium powder can be mixed with enough daily ration for four puppies (USP, 1998). Amprolium should be provided in either the food or in the water but not in both for a period of 7 days. It may be given as a treatment for coccidia or as a preventative for 7 days before puppies are shipped or to bitches just before whelping.

Cats may be treated at a dose of 60 to 100 mg/kg by mouth once daily for 7 days, which may be accomplished by direct oral administration (Dubey and Greene, 1998). Placement of medication in food or water may be more unreliable for cats than for dogs due to the finicky tastes of cats.

Furazolidone

Although the nitrofurans (nitrofurazone and furazolidone) have been reported in the literature as being effective in the treatment of coccidiosis and were once widely available for oral treatment of food animals, they have been systematically eliminated from the veterinary marketplace in the United States due to concerns regarding carcinogenicity. Furazolidone apparently inhibits numerous microbial enzyme systems, especially those related to carbohydrate metabolism, but the actual mechanism of action remains to be determined (Fraser et al., 1991). Furazolidone is still available in a dosage form that is approved for human use (Furoxone). Potential toxicity includes gastrointestinal disturbance, peripheral neuritis, decreased spermatogenesis, and weight gain (Brander et al., 1991). Dogs and cats can be treated with 8 to 20 mg/kg orally, one to two times daily, for 5 days (Dubey and Greene, 1998; Plumb, 1999). The product is available in two formulations approved for use in people (Furoxone): 100-mg tablets and an oral liquid containing 3.34 mg/mL.

Quinacrine

Quinacrine has demonstrated useful activity in the treatment of coccidiosis. Unfortunately U.S. commercial production of the drug (Atabrine) was discontinued in 1993.

TOXOPLASMOSIS

Biology

Toxoplasmosis is caused by *Toxoplasma gondii,* an obligate intracellular coccidian parasite. The parasite and the disease occur worldwide and have serious zoonotic impact. The domestic cat and other cats serve as the definitive hosts of this parasite. All other warm-blooded animals serve as intermediate hosts. In the United States, infection rates range from 0% to 100% in cats, 30% in dogs, and 30% to 60% in people. Although infection and seroconversion are common, clinical disease and diagnosis is rare (Taboada and Merchant, 1995).

Enteroepithelial Life Cycle

The enteroepithelial life cycle of *T. gondii* in cats is similar to the life cycle of the common enteric coccidia (Fig. 14–2). *Toxoplasma* oocysts are ingested from the environment; alternatively, tissue cysts may be ingested by carnivorism. Once ingested, bradyzooites are released that penetrate the epithelial cells and begin a cycle of asexual reproduction. The sexual stage of the cycle proceeds when the zooites differentiate into microgametes and macrogametes. The macrogametes are fertilized by the microgamete, and the resulting union produces an oocyst that is shed in the feces to begin the cycle again. It is believed that the enteroepithelial life cycle and the resulting oocysts only occur in cats; therefore, only cats shed infective oocysts.

Extraintestinal Life Cycle

The extraintestinal life cycle occurs in all warm-blooded animals, including cats. This cycle begins when oocysts or infected tissues are ingested. The bradyzoites or sporozoites penetrate intestinal cells and undergo asexual reproduction and then break out of the gastrointestinal tract to infect virtually all other tissues, including the brain, striated muscle, and liver. After entering these extraintestinal tissues, they penetrate the cell and multiply until the cell is destroyed. The tachyzoites are released to infect other cells, and the cycle repeats. Eventually the tachyzoites form tissue cysts that remain viable and infective for the life of the animal. These tissue cysts are infective to all warm-blooded animals and infect all animals who ingest the infected tissues. It is the ubiquitous tissue migration and replication across innumerable species that makes the pathogen so insidious and dangerous.

Congenital Transmission

If the host is infected during pregnancy, then the tachyzoites move across the placenta to infect the developing fetus. Infection during the first half of the pregnancy leads to more severe disease in the fetus. Women infected during pregnancy risk congenital malformation, mental retardation, or death of their unborn fetus. Women should be cautioned to avoid exposure to cat feces and to avoid consuming undercooked meat during pregnancy.

Clinical Signs

Clinical signs in cats are most severe in prenatally infected kittens. Such kittens may be stillborn or die before wean-

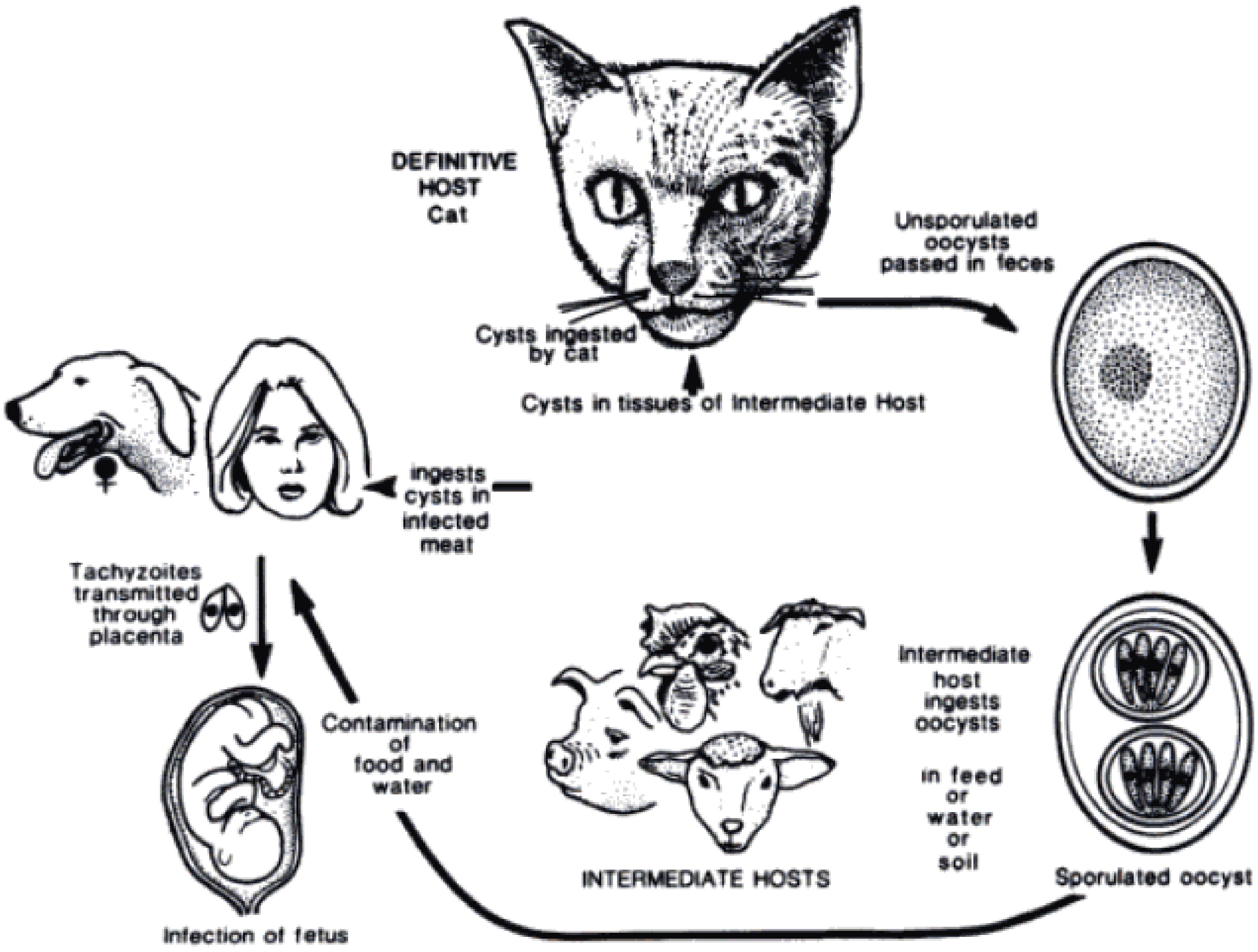
DEFINITIVE HOST Cat
Unsporulated oocysts passed in feces
Cysts ingested by cat
Cysts in tissues of Intermediate Host
ingests cysts in infected meat
Tachyzoites transmitted through placenta
Contamination of food and water
Intermediate host ingests oocysts
in feed or water or soil
INTERMEDIATE HOSTS
Sporulated oocyst
Infection of fetus

Figure 14–2. Life cycle of *Toxoplasma gondii*. (From Dubey JP, Lappin MR: Toxoplasmosis and neosporosis. *In* Greene CE [ed]: Infectious Diseases of the Dog and Cat [2nd ed], p. 494. Philadelphia, WB Saunders, 1998.)

ing. Clinical signs relate to pathology in the liver, lungs, and central nervous system. Adult cats typically demonstrate anorexia, lethargy, dyspnea, weight loss, icterus, vomiting, diarrhea, stiff gait, shifting leg lameness, and neurologic deficits. Ocular lesions may include uveitis in the anterior and posterior chambers, iritis, iridocyclitis, and detached retinas. In severe cases, respiratory or central nervous system involvement may cause death (Dubey and Lappin, 1998).

Infected dogs may show clinical signs related to respiratory, neuromuscular, or gastrointestinal pathology. Generalized toxoplasmosis is characterized by fever, tonsillitis, dyspnea, diarrhea, and vomiting (Dubey and Lappin, 1998). More devastating clinical signs may be seen in dogs with neurologic or muscular involvement. Seizures, neurologic deficits, tremors, ataxia, paresis, or paralysis may be seen in these animals. Ocular lesions in dogs are infrequently reported (Dubey and Lappin, 1998).

Diagnosis

Antemortem diagnosis of toxoplasmosis is a significant diagnostic challenge due primarily to the usual lack of clinical signs in infected animals. Fecal floatation for infected cats may reveal small oocysts that are indistinguishable from other coccidia. It is also important to realize that infected cats shed oocysts for only 1 to 2 weeks after their first exposure, thereafter forming a protective immunity that prevents further shedding of oocysts. Many other tools have been applied to the diagnosis of toxoplasmosis, including clinical chemistry, which may reveal elevated liver enzymes; cytology, which may detect tachyzoites; radiology, which could suggest inflammation of target organs; serology, which would reveal a past infection; and parasite isolation. Unfortunately, no simple, specific, and timely diagnostic tool is available to detect an active case of toxoplasmosis.

Treatment

Treatment of toxoplasmosis may have several goals: to prevent shedding of oocysts from infected cats, to prevent transmission of toxoplasmosis by ingestion of infected tissues, to prevent tachyzoite replication in nonfeline host tissues, and to prevent prenatal infections. In some cases the goal may be to alleviate clinical signs of an active infection.

Clindamycin

Clindamycin is currently considered the drug of choice for treating toxoplasmosis. Structurally, clindamycin is a congener of lincomycin. Clindamycin is well absorbed (90%) after oral administration and is widely distributed in most tissues, except the central nervous system. It readily crosses the placenta and is extensively bound to plasma proteins. The drug is metabolized in the liver and excreted primarily in the urine and bile (Hardman et al., 1996). Gastrointestinal upset is sometimes reported in animals receiving clindamycin. Severe, even fatal, pseudomembranous enterocolitis has been reported in people, caused by overgrowth of *Clostridium difficile*.

Treatment of systemic *Toxoplasma* infection in dogs can be accomplished with oral or intramuscular clindamycin at 10 to 20 mg/kg twice daily for 2 weeks (Dubey and Lappin, 1998; Greene et al., 1985). Cats can be treated for systemic infections with oral or parenteral clindamycin at 10–12.5 mg/kg twice daily for 2 to 4 weeks; this antibiotic is also useful to control shedding of oocysts (Lappin et al., 1989). The drug should be given with caution to cats with pulmonic toxoplasmosis; parenteral administration to experimentally infected cats resulted in several deaths (Plumb, 1999).

Clindamycin is available in two veterinary formulations (Antirobe): capsules containing 25, 75, or 150 mg and an oral solution containing 25 mg/mL. Similar clindamycin formulations are available for use in people (Cleocin): 75- and 150-mg oral capsules, an oral pediatric suspension (15 mg/mL), and an injectable solution containing 150 mg/mL.

Sulfa Plus Pyrimethamine

The more time-tested therapeutic regimen for toxoplasmosis is a combination of sulfonamide and pyrimethamine. The sulfonamides are discussed earlier. Pyrimethamine is structurally and pharmacologically similar to the folic acid antagonist trimethoprim. Pyrimethamine is primarily used in veterinary medicine to treat toxoplasmosis and equine protozoal myelitis "equine toxoplasmosis." Little pharmacokinetic data are available for pyrimethamine in dogs and cats, but in people it is well absorbed after oral administration. It is well distributed to the kidneys, liver, spleen, and lungs. The metabolic pathway is unclear, but pyrimethamine metabolites may be found in the urine.

Pyrimethamine can cause anorexia, malaise, vomiting, depression, and myelosuppression. Concomitant oral administration of folinic acid or brewer's yeast may help alleviate some of these clinical signs. Because toxicity may develop rapidly in cats, they should have frequent hematologic monitoring. It is a teratogen in rats but is sometimes used by pregnant women (Plumb, 1999).

Dogs and cats are treated for systemic *Toxoplasma* infections at a dose of 30 mg/kg sulfa and 0.25 to 0.5 mg/kg pyrimethamine orally twice daily for 2 weeks. Cats may be treated to control shedding of oocysts at a dose of 100 mg/kg sulfa and 2 mg/kg pyrimethamine orally once per day for 1 to 2 weeks (Dubey and Lappin, 1998).

Pyrimethamine alone is available in 25-mg tablets (Daraprim) and in combination tablets containing 25 mg pyrimethamine and 500 mg sulfadoxine (Fansidar). These dosage forms are likely to be difficult for most cat owners to administer.

Monensin

Monensin is an ionophore coccidiostat that is fed to poultry and cattle to enhance feed efficiency. It forms ionic complexes that move across biological membranes. The net effect is disturbance of mitochondrial function, which inhibits growth of the pathogen. It is not well absorbed from the gastrointestinal tract, and thus oral administration provides effective concentrations only in the gastrointestinal tract. It can be toxic if high doses are given. Shedding of *Toxoplasma* oocysts may be controlled in cats by mixing monensin in the feed at 0.2% on a dry matter basis and feeding for 1 to 2 weeks (Dubey and Lappin, 1998). Monensin is available in several feed-additive formulations designed for incorporation into a finished feed. Formulating such feeds for cats is beyond the capabilities of most cat owners.

GIARDIA

Biology

Giardia (*Giardia duodenalis* = *Giardia lamblia*) are protozoan parasites that are motile by means of flagella. They exist extracellularly in the lumen of the gastrointestinal tract. They are ubiquitous pathogens that can inhabit and cause disease in most mammals and are well-known pathogens in dogs, cats, and people. Recent surveys show that 36% of puppies in the United States are infected with *Giardia* (Hahn et al., 1988). Despite this prevalence, the condition in pet animals remains underdiagnosed due to inappropriate fecal examination techniques. It is a pathogen with zoonotic potential, as *Giardia* frequently causes disease in people, but there is some uncertainty as to whether the same species and strains infect people and pets. More extensive information about this issue can be found elsewhere (Barlough, 1979; Barr, 1998; Bowman, 1999; Kirkpatrick, 1986; Zajac, 1992).

The life cycle of *Giardia* is direct and simple (Fig. 14–3). The cyst of the *Giardia* is passed in the feces. It is nonmotile and protected by a distinct wall. Although very susceptible to drying, the cysts can survive for weeks or months in cool water. Infections are often traced back to contaminated drinking water. Once ingested, the cysts break open and trophozoites are released into the small intestine. The trophozoites are flattened on one side with a ventral sucking disk that attaches to the brush border surface of the villous epithelium. The trophozoites obtain their nutrients via the host cell membrane. The flagella provide locomotion from one attachment site to another. The trophozoites reproduce by binary fission. After several divisions the trophozoites encyst and are shed in the feces; they are immediately infective.

Conventional fecal floatation techniques make identification of the parasite difficult because concentrated salt floatation media distort the trophozoites. Preferred methods of diagnosis include microscopic examination of saline smears, which readily show the motile trophozoites. Alternatively, a zinc sulfate centrifugal method may be used to concentrate the giardial cysts and improve sensitivity (Bowman, 1999). Improved techniques for evaluation of duodenal aspirates and fecal ELISA testing have recently become available.

Treatment

Albendazole

Albendazole is a broad-spectrum benzimidazole commonly used for treatment of nematode and trematode infections in large animals. Early evidence suggested that albendazole

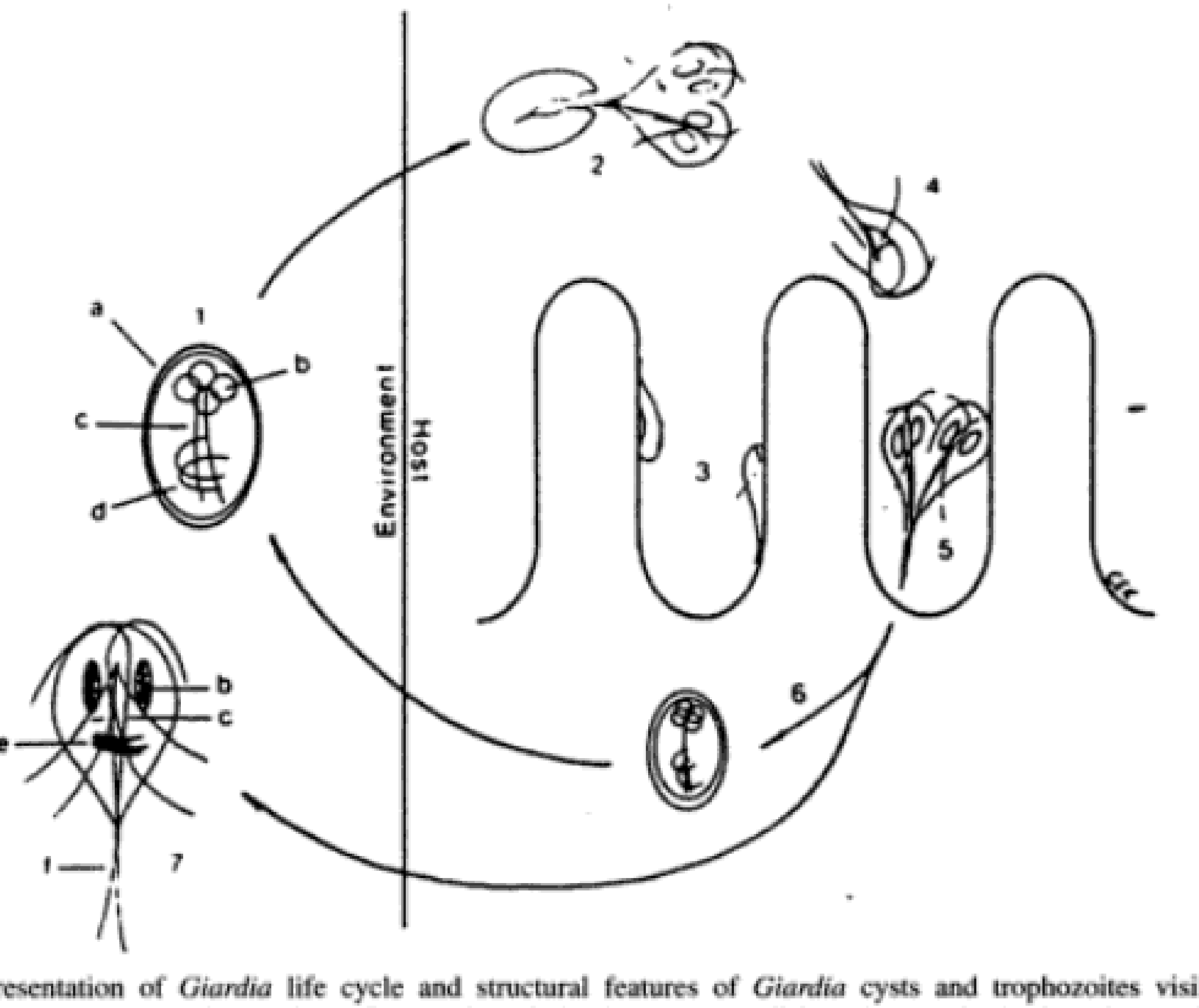

Figure 14–3. Schematic representation of *Giardia* life cycle and structural features of *Giardia* cysts and trophozoites visible by light microscopy. Infection begins when a cyst *(1)* is ingested by the host. Excystation *(2)* in the upper small intestine results in the release of an incompletely divided pair of trophozoites. Trophozoites attach to villous epithelial surfaces *(3)* or swim freely *(4)* in the lumen of the small intestine, where asexual division of trophozoites *(5)* also takes place. Encystment *(6)* of trophozoites, probably in the lower ileum or in the colon, results in the passage of infective cysts in the feces. Trophozoites *(7)* may also be passed into the environment, but they die quickly. Key to organelles: *a,* cyst wall; *b,* nuclei; *c,* axonemes; *d,* adhesive-disc fragments; *e,* median bodies; and *f,* flagella. (From Kirkpatrick CE: Giardiasis. Vet Clin North Am Small Anim Pract 1987; 17: 1377.)

is 100% effective in treating giardiasis in dogs (Barr et al., 1993). The dose given in that study was 25 mg/kg orally twice a day for four doses. Albendazole is available in an oral suspension (Valbazen) containing 113.6 mg/mL.

Albendazole, like other benzimidazoles, is well absorbed (about 50% bioavailable) and converted in the liver to its active metabolites, albendazole sulfoxide and albendazole sulfone. These active metabolites are thought to bind to tubulin molecules, which prohibits the formation of microtubules and disrupts cell division. There is also evidence that benzimidazoles can inhibit fumarate reductase, which blocks mitochondrial function, thus depriving the parasite of energy and resulting in death. The parent drug and its metabolites are excreted primarily in the urine.

Albendazole has been shown to be teratogenic, thus limiting its use in pregnant animals. Dogs treated with 50 mg/kg twice daily may develop anorexia, and cats treated with 100 mg/kg per day for 14 to 21 days showed weight loss, neutropenia, and mental dullness (Plumb, 1999). More recently, the drug was shown to be toxic to dogs and cats in clinical use (Meyer, 1998; Stokol et al., 1997). Reported toxicities include myelosuppression (anemia, leukopenia, and thrombocytopenia), abortion, teratogenicity, anorexia, depression, ataxia, vomiting, and diarrhea. Veterinarians are advised to use due caution with this product in dogs.

Fenbendazole

Fenbendazole is currently approved by the U.S. Food and Drug Administration for removal of gastrointestinal helminths in dogs. Recently, it has shown excellent activity against *Giardia* (Barr et al., 1994; Meyer, 1998; Zajac et al., 1998). The approved dose and the effective dose against *Giardia* is 50 mg/kg orally once daily for 3 days. Treatment of giardiasis is not an approved use for this product.

The drug is well tolerated and has a good safety profile. The only reported adverse effects are vomiting and diarrhea. This time tested anthelmintic should enjoy more widespread use in the treatment of *Giardia* in dogs.

Furazolidone

There is a report of successful treatment of giardiasis in cats with furazolidone (Kirkpatrick, 1985). As noted above, furazolidone was once widely available for oral treatment of food animals. Presently, the nitrofurans have been systematically eliminated from the veterinary marketplace in the United States due to concerns regarding carcinogenicity. Furazolidone is still available in a dosage form that is approved for human use (Furoxone). Toxicity includes gastrointestinal disturbance, peripheral neuritis, decreased spermatogenesis, and weight gain (Brander et al., 1991). Cats can be treated with a dose of 4 mg/kg two times daily for 7 to 10 days (Barr, 1998; Sherding and Johnson, 1994). The product is available in two formulations approved for use by people (Furoxone), 100-mg tablets and an oral liquid containing 3.33 mg/ml.

Metronidazole

The nitroimidazoles represent a very useful class of drugs that have broad-spectrum activity against trichomonads, amebas, *Giardia*, as well as anaerobic cocci and *Bacillus* species. The prototypical nitroimidazole is metronidazole, which has become the drug of choice for treatment of *Giardia*. Other drugs in the class (ipronidazole, tinidazole, nimorazole, ornidazole, and benznidazole) have been used to control *Giardia*, although none are currently available in the United States. None of the nitroimidazole drugs is approved for use in animals. The FDA strongly warns against their use in food-producing animals, as this class of drug has been shown to produce tumors in laboratory rodents.

Metronidazole (Flagyl) is well absorbed from the gastrointestinal tract. It has very low protein binding and is well distributed in the body. After entering the target cell it interacts with the protozoal DNA, where it causes a loss of helical structure and strand breakage (USP, 1998). The liver extensively metabolizes the drug, and in humans hepatic transformation is responsible for 50% of the elimination. Patients receiving cimetidine or phenobarbital may require adjustment in the dosage due to drug interaction. Metronidazole toxicity may be seen with high doses. Neurologic toxicity includes ataxia, nystagmus, seizures, tremors, or weakness (USP, 1998; Dow et al., 1989). Numerous studies have demonstrated that metronidazole is an effective treatment for giardiasis (Boreham et al., 1984; Kirkpatrick and Farrell, 1984; Zimmer, 1987; Watson, 1980; Zimmer and Burrington, 1986), although efficacy is rarely 100%. Dogs may be treated orally with 12.5 to 32.5 mg/kg twice daily; therapy should be continued for 8 days. Cats may be treated orally with 17.4 mg/kg once daily for 8 days (USP, 1998). The commercially available product (Flagyl) is formulated in 250- and 500-mg tablets. Parenteral formulations are also available, but their usefulness would seem questionable considering that the giardial trophozoites remain in the lumen of the gastrointestinal tract.

Quinacrine

Quinacrine as described above has also been shown to be useful in treating giardiasis in dogs and cats (Zimmer and Burrington, 1986). Unfortunately, commercial production of the product (Atabrine) was discontinued in 1993.

SUMMARY

Therapy of protozoal infections in small animals may range from simple to complex therapeutic dilemmas. The best treatment of each case must be determined by considering the life cycle of the pathogen, the general physical condition of each animal, and the animal's environment. Therapy must include adequate attention to supportive therapy to control clinical signs and to support normal body function. Therapy also include adequate hygiene to limit reinfection and disease transmission. The selection and administration of the specific antiprotozoal agent is only one part of the overall therapeutic picture.

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15

Drugs for the Treatment of Helminth Infections

Randy C. Lynn

INTRODUCTION
ANTHELMINTICS
Macrolides
  Ivermectin
  Milbemycin Oxime
  Moxidectin
  Selamectin
Benzimidazoles
  Albendazole
  Febantel
  Fenbendazole
  Oxibendazole
  Thiabendazole
Levamisole
Pyrantel
Piperazines
  Piperazine
  Diethylcarbamazine
Organophosphates: Dichlorvos
Isoquinolones
  Praziquantel
  Epsiprantel
Arsenicals
  Thiacetarsamide
  Melarsomine
Miscellaneous Anthelmintics
  Dichlorophen
  N-Butyl Chloride
  Toluene
BROAD-SPECTRUM COMBINATIONS
Dichlorophen Plus Toluene
Diethylcarbamazine Plus Oxibendazole
Febantel Plus Praziquantel
Febantel Plus Praziquantel Plus Pyrantel
Pyrantel Plus Praziquantel
Ivermectin Plus Pyrantel Pamoate

INTRODUCTION

Gastrointestinal parasites are among the most common infectious agents that veterinarians in small animal practice must manage (Blagburn et al., 1996). In the landmark parasite prevalence study, Blagburn and coworkers evaluated over 6000 canine fecal specimens from all 50 states and the District of Columbia. The results indicate that parasites remain common in American dogs. Nationwide 36% of the samples tested were positive for roundworm (*Toxocara canis*), hookworm (*Ancylostoma caninum*), or whipworm (*Trichuris vulpis*). Even more surprising, 52% of the samples from the southeastern United States were positive for at least one of the important nematodes. Although these parasites are important to the health of dogs, several are also important zoonotic pathogens.

The life cycle and biology of the most important parasites are well understood by graduate veterinarians and are not discussed here; however, current textbooks of parasitology may be consulted for review (Bowman, 1999; Georgi and Georgi, 1992). The literature on antiparasite drugs is enormous; in the interests of both economy and readability, only a few references are listed. These will guide the veterinarian who needs more specific information about the subject. Tables 15–1 and 15–2 provide a general overview of anthelmintic drug spectrum against the common gastrointestinal nematodes. The text should be consulted for specific dosage regimens, toxicity, and contraindications.

A parasiticide is a poison that is more toxic to parasites than to their hosts. The degree of discrimination is sometimes small, sometimes considerable, but never complete, so that application of parasiticides always entails some hazard to the host. As a matter of fact, it is sometimes easier to explain the deleterious effects that parasiticides exert on the host than to explain how they kill parasites.

ANTHELMINTICS

An exhaustive review of the pharmacology, mechanism of action, pharmacokinetics, and efficacy of anthelmintics is outside the scope of this book. For more exhaustive information on anthelmintics, there are two excellent works that should be consulted (Campbell and Rew, 1985; Vanden Bossche et al., 1985). A compendium of products approved by the U.S. Food and Drug Administration (FDA) and commercially available can be found in the Veterinary Products and Biologics (Entriken et al., 1998).

Macrolides

Macrolides (or macrocyclic lactones) have revolutionized the control of parasites in both humans and animals. They are generally regarded as the most effective and least toxic parasiticides yet developed. These products are similar in that they are antibiotics produced by streptomycete microorganisms and have large complex macrocyclic structures. Although originally believed to act by disturbing gamma-aminobutyric acid (GABA)–mediated neurotransmission, it now appears that they act with high affinity to a glutamate-gated chloride channel (Shoop et al., 1995). The macrocyclic lactones apparently trigger chloride ion influx, which hyperpolarizes the parasite neuron and prevents initiation or propagation of normal action potentials. The net effect is paralysis and death of the target parasite. The literature surrounding these products is considerable, but several good reviews pare the literature down to comprehensible levels (Bennett, 1986; Campbell, 1989; Shoop et al., 1995).

Ivermectin

Ivermectin was the first commercially available macrolide. The avermectins were isolated from the fermentation broth

Table 15–1. Canine Anthelmintic Medication*

	Common Canine Parasites								
				Tapeworm			Heartworm		
Drug	**Roundworm**	**Hookworm**	**Whipworm**	D	T	E	Prev.	Mff	Adult
Macrocyclics									
Ivermectin	+	+					+	+	
Milbemycin oxime	+	+	+				+	+	
Moxidectin	+	+					+	+	
Selamectin							+		
Benzimidazoles									
Febantel	+	+	+						
Fenbendazole	+	+	+		+				
Oxibendazole	+	+	+						
Levamisole								+	
Pyrantel	+	+							
Piperazines									
Piperazine	+								
Diethylcarbamazine							+		
Dichlorvos	+	+	+						
Isoquinolones									
Praziquantel				+	+	+			
Epsiprantel				+	+				
Arsenicals									
Thiacetarsamide									+
Melarsomine									+
Miscellaneous									
Dichlorophene				+	+				
N-butyl chloride	+	+							
Toluene	+	+							

*Tapeworm Genera. D = *Dipylidium*; T = *Taenia*; E = *Echinococcus*. Heartworm Agents. Prev. = prevention; Mff = microfilaricide; Adult = adulticide. Some activities listed are not approved or require higher than approved doses.

of *Streptomyces avermitilis*. The discovery of the anthelmintic activity was made after administration of the actinomycetic broth to mice infected with the nematode *Nematospiroides dubius*. Ivermectin is effective against many nematodes and arthropods. In particular, ivermectin is very effective against immature *Dirofilaria immitis* but has minimal effect on adult heartworms. Administration of ivermectin to pregnant rats, mice, and rabbits produced teratism only at or near maternotoxic doses. There was no teratogenesis in cattle, sheep, and dogs when ivermectin was administered to pregnant animals at four times the recommended dose. Although toxicity for aquatic animals is high, the binding of ivermectin in soil reduces its concentration to levels that have no apparent effect on the environment. The acute oral LD_{50} in mice varied from 11.6 to 87.2 mg/kg and the LD_{50} for rats was 42.8 to 52.8 mg/kg. In a 14-week study with rats, the "no-effect" level was 0.4 mg/kg.

Ivermectin is well absorbed (95%) after oral administration and well distributed to most tissues except the central nervous system. It is largely eliminated unchanged in the feces and is metabolized to a small degree in the liver by oxidation. In dogs the terminal half-life is approximately 48 hours.

A single oral dose of 2 mg/kg and repeated oral doses of 0.5 mg/kg per day for 14 weeks were well tolerated by dogs (Paul and Tranquilli, 1989). Mydriasis, depression, tremors, ataxia, coma, and death have been observed after doses in excess of 40 mg/kg in laboratory dogs. The apparent LD_{50} for beagle dogs is 80 mg/kg (Paul and Tranquilli, 1989). No teratism was observed in fetuses when pregnant bitches received repeated oral doses of ivermectin of 0.5 mg/kg.

Some collie dogs are unusually sensitive to the toxic effects of ivermectin, although it is safe for all breeds at the approved dose of 6 μg/kg. Early studies indicated that some genetic lines of collie developed severe adverse reactions when ivermectin was given at a dose of 0.1 mg/kg (16 times the label dose), producing mydriasis, ataxia, tremors, drooling, paresis, recumbency, excitability, stupor, and coma. There is some evidence that intravenous administration of physostigmine may be of some benefit for dogs suffering from severe ivermectin intoxication (Tranquilli et al., 1987), although the mainstay of therapy remains supportive and symptomatic therapy (Paul and Tranquilli, 1989).

Dogs Ivermectin (Heartgard) tablets are administered orally at a dose level of 0.006 mg/kg (6 μg/kg) at monthly intervals to prevent the establishment of the *D. immitis*. The initial dose should be given within 1 month after the first exposure to mosquitoes and throughout the period of the year when mosquitoes are active. The last treatment must be given to dogs within 1 month after the last exposure to mosquitoes. Ivermectin has minimal activity against

Table 15-2. Feline Anthelmintic Medication*

	Common Feline Parasites				
			Tapeworm		
Drug	***Roundworm***	***Hookworm***	D	T	***Heartworm Prev.***
Macrocyclics					
Ivermectin	+	+			+
Milbemycin oxime		+			+
Selamectin	+	+			+
Benzimidazoles					
Febantel	+	+			
Fenbendazole	+	+			
Mebendazole	+	+			
Pyrantel	+	+			
Piperazine	+				
Dichlorvos	+	+			
Isoquinolones					
Praziquantel			+	+	
Epsiprantel			+	+	
Miscellaneous					
Dichlorophene			+	+	
N-butyl chloride	+	+			
Toluene	+	+			

*Tapeworm genera. D = *Dipylidium*; T = *Taenia*. Heartworm agents. Prev. = prevention. Some activities listed are not approved or require higher than approved doses.

the adult heartworm. It is active on the third-stage and fourth-stage larvae and the circulating microfilariae. A single oral dose of ivermectin administered within 2 months after infection prevents the establishment of the worms in the heart. A single dose of 0.05 mg/kg is adequate to clear the circulating microfilariae when given to dogs 4 weeks after the administration of an adulticide. Ivermectin is not approved as a microfilaricide. When ivermectin (0.006 mg/kg) is given to heartworm-positive dogs over several months, the circulating microfilariae are eliminated, resulting in an occult infection. Thus dogs receiving ivermectin monthly should be tested annually with an occult heartworm test (Bowman et al., 1992).

When diethylcarbamazine is replaced in a preventative program, the first dose of Heartgard must be given within 1 month after diethylcarbamazine is stopped. Heartgard should not be given to dogs under 6 weeks of age.

Ivermectin as a single subcutaneous injection or by oral administration at 0.2 mg/kg demonstrated high efficacy against the immature and adult *T. canis*, *A. caninum*, *A. braziliense*, *Uncinaria stenocephala*, *Strongyloides stercoralis*, *Capillaria* spp., and *Filaroides hirthi* (Bowman, 1999; Plumb, 1999). Its activity at that dose against *Toxascaris leonina* and *T. vulpis* is erratic.

A combination product (Heartgard plus) containing ivermectin and pyrantel pamoate is available. See the discussion of combination products for more information.

Cats Ivermectin is approved as a monthly heartworm preventative in cats (Heartgard for cats). The approved dose of 0.024 mg/kg is effective in preventing the development of *D. immitis* (McTier et al., 1992b; Paul et al., 1992a). It is also approved for use against *A. braziliense* and *A. tubaeforme* (Nolan et al., 1992, Roberson et al., 1992). A dose of 0.3 mg/kg is required to eliminate *Toxocara cati* (Blagburn et al., 1987, Kirkpatrick and Megella, 1987).

Milbemycin Oxime

Milbemycin oxime was the second macrocyclic lactone to achieve approval by the U.S. FDA. It is a fermentation product of *Streptomyces hygroscopicus aureolacrimosis.* It has structural similarities to ivermectin and is believed to work by a similar mechanism of action. Little is known about its pharmacokinetics. It is generally believed to be similar to ivermectin with regard to absorption, metabolism, and excretion. Although an LD_{50} was never determined for dogs, single oral doses of 200 mg/kg were tolerated in laboratory beagles, and collie dogs tolerated single oral doses of 10 mg/kg without toxicity.

Dogs Milbemycin oxime tablets (Interceptor) are formulated to deliver a minimum dose of 0.5 mg/kg of body weight. When given every 30 days it is effective in preventing heartworms (*D. immitis*) (Bater, 1989; Bradley, 1989; Grieve et al., 1991). It also kills *A. caninum*, *Toxocara canis*, and *Trichuris vulpis* (Blagburn et al., 1992c; Bowman et al., 1988, 1990, 1991). Milbemycin oxime has been extensively tested with regard to safety. It is nontoxic to collies at up to 20 times the recommended dose and is safe to give to pregnant and nursing animals (Blagburn et al., 1989; Sasaki et al., 1990).

Milbemycin oxime, like ivermectin, is known to kill heartworm microfilariae and inhibit the release of new microfilariae. Thus all dogs receiving routine monthly heartworm prophylaxis should be tested with adult antigen tests (Blagburn et al., 1992a; Bowman et al., 1992; Lok et al., 1992).

Cats Milbemycin oxime is approved for use in cats (Interceptor for Cats). The product is effective in preventing *Dirofilaria* (Stewart et al., 1992) and effective in removing *T. cati* and *A. tubaeforme* (Blagburn et al., 1992b) when given once a month at a dose of 1.5 mg/kg.

Moxidectin

Moxidectin is the third macrolide to enter the parasite market. It is currently approved in the United States for use in dogs (Proheart). It is a chemically altered product of *Streptomyces aureolacrimosus noncyanogenus.* It has a similar range of activity and safety margin as ivermectin and milbemycin oxime.

Dogs Moxidectin is known to be very active against heartworms (*D. immitis*) and gastrointestinal nematodes. It is approved for the prevention of heartworms at a dose of 0.003 mg/kg (3 µg/kg) orally every month. When moxidectin is administered at 0.003 mg/kg of body weight monthly it is 100% effective in preventing the development of adult *D. immitis* (McCall et al., 1992; McTier et al., 1992a; King et al., 1992). At the recommended dose it is safe in rough-coated collies (Paul et al., 1992b), and it produced no adverse effects in collie dogs when given at 20 times the approved dose, although mild toxic effects were seen at 30 times the approved dose (Anonymous, 1997). Moxidectin showed little effect on the circulating microfilariae of *D. immitis* in a short-term study (Hendrix et al., 1992), although the long-term effects on microfilariae remain to be published. It produced no adverse reactions in dogs with patent heartworm infection, although the approved label prohibits use for such dogs (Anonymous, 1997).

Moxidectin is also effective against gastrointestinal nematodes. It is effective against *A. caninum* at 0.025 mg/kg and against *U. stenocephala* at 0.15 mg/kg. It also demonstrated good activity against *Toxocara canis* and *Toxascaris leonina* at the doses tested (0.025 to 0.3 mg/kg orally) (Supakorndej et al., 1993).

Selamectin

Selamectin (Revolution) is the latest macrolide to enter the United States marketplace. It is currently approved for use in dogs and cats to control both internal and external parasites. This product is unique among other macrolides used in small animals in that it is formulated for convenient topical administration. It is simply "spotted" onto the skin of the pet.

This discussion is limited to selamectin's use against internal parasites. It is produced as a fermentation product of *Streptomyces avermitilis* which is then chemically modified (Thomas, 1999). The pharmacokinetics after topical administration has been studied extensively. The topical bioavailability varies greatly among species. In dogs the bioavailability is only 4%, but it is much bigger (74%) in cats. The terminal half-life was much longer in both species after topical administration than after intravenous administration, which suggests sustained release from an extravascular depot. The half-life after topical administration was 11 days for dogs and 8 days for cats. The product is absorbed in sufficient quantities and persists for sufficient time to control the target parasites. The approved topical dose is a minimum of 6.2 mg/kg for dogs and is 6.6 mg/kg for cats.

Selamectin is approved for the prevention of heartworm *(Dirofilaria immitis)* in both dogs and cats when applied topically once every 30 days (McTier et al., 1998). Extensive studies have proved the drug's efficacy against heartworms (Thomas, 1999), even when application was followed by bathing. The bathing study demonstrated that the topical application is not likely to be dislodged by inadvertent swimming or rainstorms. In cats, selamectin is also effective in removing hookworm *(Ancylostoma tubaeforme)* and roundworm *(Toxocara cati)*. This effect is undoubtedly owing to the greater topical bioavailability observed in cats (Thomas, 1999).

The safety of selamectin has been established in both dogs and cats and even for use in puppies and kittens over 6 weeks old. It is also safe to use in breeding dogs and cats (Thomas, 1999). Most important, the safety was demonstrated in ivermectin-sensitive collie dogs. There is no label warning against its use in heartworm-positive dogs and cats. Clinical studies have confirmed the wide safety margin demonstrated in the laboratory studies.

Benzimidazoles

The benzimidazoles represent a large family of broad-spectrum agents that have enjoyed widespread use for many years in a wide array of animal species. Excellent review articles (Campbell, 1990; Lacey, 1990; McKellar and Scott, 1990) discuss the history, mode of action, and spectrum of activity of this useful class of anthelmintics.

Thiabendazole was the first benzimidazole discovered, and it represented a major step forward when it became available over 30 years ago. At the time of its introduction, thiabendazole was a true broad-spectrum product that was very safe to the host animal. Since that time, parasite resistance to the benzimidazoles has been discovered in several species of large-animal parasites.

Considerable effort has been devoted to determining the mechanism by which the benzimidazoles act on parasites. Conventional wisdom holds that benzimidazoles bind to tubulin molecules, which inhibits the formation of microtubules and disrupts cell division. Evidence also indicates that the benzimidazoles can inhibit fumarate reductase, which blocks mitochondrial function and kills the parasite by depriving it of energy.

The benzimidazoles are poorly soluble and thus are generally given by mouth. They are more effective in horses and ruminants due to their slow transit through the cecum and rumen. Proper use in small animals requires that the benzimidazoles be given for a minimum of 3 days in a row. The dose is usually more effective when divided into two doses per day, thus prolonging the contact time with the parasite.

One member of the group, albendazole, has been found to be teratogenic, thus limiting its use in pregnant animals. For simplicity the pro-benzimidazole drug febantel is included in this section. It is a nonbenzimidazole drug that is metabolized to a benzimidazole; thus it shares a similar efficacy and mechanism of action with the other benzimidazoles.

Albendazole

Albendazole is the newest benzimidazole, with potent broad-spectrum anthelmintic activity. Albendazole (Albenza) is used overseas for the treatment of intestinal helminth infections, hydatid disease, and cysticercoses of humans. It is commonly used for treatment of nematode and trematode infections in large animals (Valbazen). Albendazole has been used safely in cats for treatment of *Paragonimus kellicotti* at a dose of 50 mg/kg daily for 21 days.

Albendazole, like other benzimidazoles, is well absorbed (about 50% bioavailable) and converted in the liver to the active metabolites albendazole sulfoxide and albendazole sulfone. These active metabolites are thought to bind to tubulin and inhibit fumarate reductase. The parent drug and its metabolites are excreted primarily in the urine.

Albendazole has been shown to be teratogenic, thus limiting its use in pregnant animals. Dogs treated with 50 mg/kg twice daily may develop anorexia, and cats treated with 100 mg/kg per day for 14 to 21 days showed weight loss, neutropenia, and mental dullness (Plumb, 1999). Albendazole in clinical use has demonstrated significant toxicity, including myelosuppression (leukopenia, anemia, and thrombocytopenia), abortion, teratism, anorexia, depression, ataxia, vomiting, and diarrhea (Meyer, 1998; Stokol et al., 1997). Veterinarians are advised to use due caution with this product for dogs.

Albendazole is available in an oral suspension (Valbazen) containing 113.6 mg/mL. Dogs can be treated for *F. hirthi* at a dose of 25 to 50 mg/kg twice daily for 5 days (Georgi et al., 1978). *C. plica* can be treated at a dose of 50 mg/kg twice daily for 10 to 14 days (Brown and Barsanti, 1989) and *P. kellicotti* at a dose of 25 mg/kg twice daily for 21 days (Bowman, 1999). The same dose is effective for *Paragonimus* in cats (Plumb, 1999). Although albendazole is effective against these uncommon parasites, ivermectin and praziquantel are more convenient therapies and likely to be just as effective.

Febantel

Febantel is a pro-drug that is metabolized to fenbendazole and oxfendazole, which are undoubtedly the active parasiticides (McKellar and Scott, 1990). The oral acute toxic dose in mice, rats, and dogs is more than 10 g/kg. At oral doses above 150 mg/kg per day for 6 days, transient salivation, diarrhea, vomiting, and anorexia may be seen in dogs and cats.

Dogs Febantel (Rintal) is given by mouth to dogs at a dose of 10 mg/kg daily for 3 consecutive days. Puppies less than 6 months of age should be given a dose of 15 mg/kg.

Febantel is effective against *A. caninum, U. stenocephala, Toxocara canis, Toxascaris leonina,* and *Trichuris vulpis* (Corwin et al., 1982). Puppies less than 6 months of age should be dosed on a full stomach; adult dogs do not need to be fed or fasted. Febantel should not be administered to pregnant animals, as administration at 30 mg/kg resulted in increased abortions and fetal abnormalities. Two combination products containing febantel are discussed below.

Cats Febantel tablets (Rintal) are effective in removing *A. tubaeforme* and *Toxocara cati* when given for 3 days at a dose of 10 mg/kg in cats and a dose of 15 mg/kg in kittens less than 6 months. Kittens should be dosed on an empty stomach.

Fenbendazole

Fenbendazole is a commercially successful benzimidazole that enjoys wide usage in dogs. The oral LD_{50} for rats and mice is higher than 10 g/kg. Fenbendazole does not have embryotoxic or teratogenic effects in rats, sheep, and cattle. In the rabbit, fenbendazole was fetotoxic but not teratogenic, and no carcinogenesis was observed in lifetime studies in rats and mice. In a 6-month toxicity study in dogs, no effect was observed at 4 mg/kg or below.

Fenbendazole is a broad-spectrum anthelmintic with activity against a variety of helminth parasites of dogs, cats, and many zoo animals. Absorbed fenbendazole is metabolized to at least two active metabolites, oxfendazole sulfoxide and oxfendazole sulfone and in ruminants it is known to undergo enterohepatic cycling, which serves to prolong effective blood levels (USP, 1998). In the United States, fenbendazole is approved for control of helminth parasites of horses, cattle, and dogs.

Dogs Fenbendazole granules (Panacur) at a dose level of 50 mg/kg is mixed in the feed and given to dogs for 3 consecutive days for the removal of *Toxocara canis, Toxascaris leonina, A. caninum, U. stenocephala, Trichuris vulpis,* and *Taenia pisiformis* (Bowman, 1992; Burke and Roberson, 1978, 1979; Roberson and Burke, 1982; Roberson and Cornelius, 1983). Recently, it has shown excellent activity against giardia at the approved dose (Barr et al., 1994; Meyer, 1998; Zajac et al., 1998). Higher unapproved dose levels (50 to 100 mg/kg) for 10 to 14 days demonstrated excellent activity against the lung fluke *P. kellicotti* (Dubey et al., 1979; Plumb, 1999). Fenbendazole is relatively safe and there are no known contraindications for its use in dogs.

Cats Fenbendazole is not currently approved for use in cats. When given at a dose of 50 mg/kg for 5 days it is effective against adult *Toxocara cati, A. tubaeforme, Aelurostrongylus abstrusus, P. kellicotti,* as well as capillaria (Bowman, 1992; Roberson and Burke, 1980).

Oxibendazole

The acute oral LD_{50} for oxibendazole is greater than 10 g/kg in guinea pigs, hamsters, and rabbits and greater than 32 g/kg in mice. No adverse reactions were observed in rats and dogs treated with up to 30 mg/kg daily for 3 months. No evidence of teratogenicity or embryotoxicity was observed in rats, mice, sheep, cattle, and horses.

A combination product of oxibendazole and diethylcarbamazine is available for dogs. See the section on broad-spectrum combination products.

Thiabendazole

The discovery of thiabendazole, the first of the benzimidazoles, in 1961 marked the beginning of truly broad-spectrum anthelmintics. It is active against nematodes, fungi, and mites. It is a very safe compound, the acute oral LD_{50} for rats is 3.1 g/kg. Owing to its wide margin of safety, thiabendazole has been used in animals of all ages and in pregnant and debilitated animals. In dogs, vomiting, diarrhea, hair loss, and lethargy are possible side effects noted with high doses or long-term treatment (Plumb, 1999). Thiabendazole is available in a variety of pharmaceutical forms (suspension, bolus, paste, feed block, feed premix and top dressing pellets) and different proprietary names. In dogs it is only used systemically for treatment of the uncommon parasites *Strongyloides* and *Filaroides* (Plumb, 1999; Allen et al., 1993); it is more commonly used topically in dogs as an antifungal agent in Tresaderm for treatment of otitis externa.

Levamisole

The discovery of tetramisole in 1966 was the first in the development of the imidazothiazoles. Tetramisole was actually a racemic mixture of two optical isomers; only the L-isomer has anthelmintic activity. The active isomer was subsequently developed as levamisole. In this class of anthelmintic only levamisole is still readily available.

The imidazothiazoles act by disturbing the neuromuscular system of susceptible nematodes causing contraction and subsequent tonic paralysis (Coles et al., 1975; Coles, 1977; Vanden Bossche et al., 1985). They are also known to interfere with the fumarate reduction system, which plays a key role in mitochondrial energy production (Behm and Bryant, 1979; Vanden Bossche et al., 1985).

Levamisole is well absorbed after oral administration, and widely distributed in the body. The parent drug is extensively metabolized in the body and excreted in the urine and feces. The half-life of elimination is 3 to 4 hours in the dog (USP, 1998). It should not be administered in combination with chloramphenicol; such practice has resulted in fatality. It should not be given in combination with cholinesterase inhibitors or with pyrantel. Administration of levamisole to dogs can result in salivation, vomiting, diarrhea, neurotoxicity, agranulocytosis, dyspnea, pulmonary edema, immune-mediated skin eruptions, and lethargy. Adverse reactions in cats include hypersalivation, excitement, mydriasis, and vomiting (Plumb, 1999).

Levamisole (Levasole, Tramisol) is available as a bolus formulated for administration to sheep, they may be administered to dogs and cats. Before the advent of ivermectin, levamisole enjoyed widespread use in dogs for the elimination of heartworm microfilariae at a dose of 10 mg/kg once a day for 6 to 10 days. Since then it is primarily used by veterinarians that are reluctant to treat collies with ivermectin. It may also be used to clear capillaria at a dose of 7 to 12 mg/kg once daily for 3 to 7 days, or for *Filaroides osleri* when given for 20 to 45 days (Plumb, 1999).

Pyrantel

Pyrantel is one of the tetrahydropyrimidines, which also include morantel and the investigational compound oxantel. Members of this anthelmintic class block ganglionic neurotransmission by their cholinergic action (Aubry et al., 1970).

The tartrate salt of pyrantel is a white powder, soluble in water that is used in horses and swine. Pyrantel tartrate is well absorbed after oral administration in the rat, dog, and pig. Plasma levels peak within two to three hours and the drug is rapidly metabolized and eliminated in the urine.

The pamoate salt of pyrantel is a yellow powder, insoluble in water. It is available as a ready-to-use suspension and as tablets for dogs and horses. Pyrantel pamoate is poorly absorbed from the intestine; this phenomenon adds to its safety in very young or weak animals. Pyrantel salts are stable in solid form but photodegrade when dissolved or suspended in water, resulting in reduction of potency.

Dogs Pyrantel pamoate, as a palatable suspension, swallow tablet, or as chewable tablet (Nemex), is indicated for the removal of *T. canis, T. leonina, A. caninum,* and *U. stenocephala* from dogs and puppies (Clark et al., 1991; Jacobs, 1987b; Klein et al., 1978; Linquist, 1975; Todd et al., 1975). The recommended dose of 5 mg/kg of Nemex suspension is administered orally or mixed with a small amount of feed. For animals weighing 2.25 kg or less, the dose is increased to 10 mg/kg. Tablets may be administered directly or placed in a small portion of food. Nemex has been shown to be safe in nursing and weanling pups, pregnant bitches, males used for breeding, and dogs infected with *D. immitis.* The oral LD_{50} is greater than 690 mg/kg in dogs. No significant morphologic changes were induced in dogs given 94 mg/kg daily for 90 days. Pyrantel pamoate is compatible with organophosphates and other antiparasitic and antimicrobial agents.

Cats Pyrantel pamoate is a very safe and effective anthelmintic for use in cats with special utility against the common nematodes of kittens and young cats. It is curious that it is not yet approved for use in cats. An oral dose of 5 to 10 mg/kg is effective against ascarids, hookworms, and *Physaloptera* and should be repeated in 2 to 3 weeks (Plumb, 1999).

Piperazines

Piperazine and the piperazine analogue diethylcarbamazine (DEC) are simple heterocyclic drugs. Piperazine and DEC are believed to produce a neuromuscular blockade through disruption of cholinergic or GABA neurotransmission (Campbell and Rew, 1985; Roberson, 1988). Piperazine and DEC are quite safe to use in all species (Roberson, 1988). These drugs all share a narrow spectrum of action and are active primarily against ascarids.

Piperazine

Various salts of piperazine (adipate, hydrochloride, sulfate, monohydrate, citrate, and dihydrochloride) are used as anthelmintics in swine, poultry, horses, dogs, and cats. Anthelmintic activity depends on freeing piperazine base in the gastrointestinal tract, thus the effective dose must be calculated on the amount of piperazine base. The amount of piperazine (base) in each salt varies widely. The citrate, adipate, phosphate, and dihydrochloride salts contain 35, 37, 42, and 50% piperazine base respectively (USP, 1998).

Piperazine paralyzes worms by blocking the action of acetylcholine and GABA at the neuromuscular junctions, and the worms are eliminated by intestinal peristalsis (Campbell and Rew, 1985; Roberson, 1988). Piperazine is also one of the active ingredients in a number of combination anthelmintic products. Piperazine should not be used in combination with pyrantel pamoate, because the modes of action are antagonistic.

Piperazine is rapidly absorbed from the gastrointestinal tract and rapidly cleared by urinary excretion. Elimination is virtually complete within 24 hours (USP, 1998). It should be used with caution in animals with hepatic or renal dysfunction. It may not be effective in animals with intestinal hypomotility because the paralyzed worms may recover from the drug effect before they are passed in the stool. Occasional adverse reactions observed in dogs include ataxia, diarrhea, and vomiting.

Piperazine is available as tablets, solution, and soluble powder under many proprietary names (Happy Jack Kennel

Wormer, Pipa-Tabs, Purina Liquid Wormer, Sergeant's Worm Away). Piperazine is practically nontoxic. The oral LD_{50} for rats is 4.9 g/kg and for mice is 11.4 g/kg. Treatment for intoxication is symptomatic and supportive. Piperazine can be administered to animals of all ages.

Piperazine is usually administered orally at 45 to 65 mg of base per kilogram (USP, 1998), although higher doses (100 to 250 mg/kg) have been reported in the literature. (English and Sprent, 1965; Jacobs, 1987a; Sharp et al., 1973). Piperazine is effective against adult roundworms *Toxocara canis, Toxocara cati,* and *Toxascaris leonina.*

Diethylcarbamazine

Diethylcarbamazine citrate (DEC) is a bitter-tasting heterocyclic compound closely related to piperazine. The drug is readily absorbed from the gastrointestinal tract and distributed to all tissues except for fat. Peak blood levels occur 3 hours after administration. Diethylcarbamazine citrate is rapidly cleared from the body (70% in 24 hours) in the urine. It is eliminated primarily as metabolites with only a small percentage (10% to 25%) excreted as unchanged drug.

Diethylcarbamazine is used almost exclusively in dogs to prevent infection with *D. immitis* at an oral dose of 6.6 mg/kg (Hawking, 1979; Knight, 1987; Kume, 1975; Kume et al., 1964, 1967; Warne et al., 1969). It is also somewhat effective as an aid in the treatment of *Toxocara canis, Toxocara cati,* and *Toxascaris leonina* infections in dogs and cats at a dose of 55 to 110 mg/kg (Vanden Bossche et al., 1985). For the prevention of heartworm infections, diethylcarbamazine is administered orally once a day at 6.6 mg/kg during the mosquito season. Puppies may be started on the prevention program for heartworm at about two months of age. It is advisable to begin administration one month before the start of mosquito season and continue until two months after the end of mosquito season. In warm climates, diethylcarbamazine should be given to dogs year round if no other means of heartworm control is available.

Diethylcarbamazine citrate is marketed under several proprietary names (Carbam, Filaribits, Nemacide) and in many pharmaceutical forms (tablets, chewable tablets, and syrup). Diethylcarbamazine is also available in combination with oxibendazole as Filaribits Plus; see the section on combination products for more information.

Warning: Dogs with circulating heartworm microfilariae may develop fatal anaphylactoid reactions if treated with diethylcarbamazine (Atwell and Boreham, 1983; Furrow et al., 1980; Hamilton et al., 1986; Palumbo et al., 1977; Powers et al., 1980). Dogs older than 6 months should be tested for microfilaremia before beginning diethylcarbamazine. All those with circulating microfilariae should be freed of adult heartworms and microfilariae before starting the diethylcarbamazine prophylactic regimen. The full therapeutic dose may cause irritation of the gastric mucosa; a light meal just before medication often reduces gastric irritation and emesis. There are anecdotal reports of sterility in male dogs but this effect has not been reproduced experimentally (USP, 1998).

Organophosphates: Dichlorvos

Dichlorvos is an organophosphate that is taken internally to kill parasites. It phosphorylates the acetylcholinesterase (AchE) enzyme. Normal AchE eliminates acetylcholine when it is released at the post-synaptic junction. When AchE is inactivated, acetylcholine accumulates at the post-synaptic junction, which results in continued depolarization. The end result is paralysis (Fest and Schmidt, 1982; Hart and Lee, 1966; Lee and Hodsden, 1963). The toxicity of organophosphates is generally related to its ability to inactivate the AchE of the host. Such toxicity is best treated with pralidoxime (2-PAM) and atropine (Woodard, 1957).

Dichlorvos is an organophosphate that is effective against many internal and external parasites. Dichlorvos is rapidly degraded in mammals. The acute oral LD_{50} for rats is 80 mg/kg. In dogs, the oral LD_{50} of unformulated dichlorvos is 28 to 45 mg/kg, whereas the formulated (resinated) dichlorvos has lower toxicity with an oral LD_{50} of 387 to 1262 mg/kg. No untoward reactions were observed in pregnant mice, rats, rabbits, sows, mares, bitches, and queens medicated with dichlorvos. Specially formulated dichlorvos is used as an anthelmintic for dogs and cats (Task, Task Tabs).

Task is a slow-release formulation of dichlorvos in non-digestible resin pellets, which are packaged in gelatin capsules and foil packets. Task is administered to dogs weighing more than 1 kg at 27 to 33 mg/kg. This should be divided and administered in two doses 8 to 24 hours apart for old and debilitated animals. Task Tabs are administered to cats and to puppies older than 10 days or weighing more than 0.5 kg at 11 mg/kg. Task and Task Tabs are indicated for the removal of adult *Toxocara canis, Toxocara cati* (Task Tabs only), *Toxascaris leonina, A. caninum, A. tubaeforme, U. stenocephala,* and *Trichuris vulpis* (Task only) (Batte et al., 1966; Howes, 1972; Olsen et al., 1977). It is interesting to note that the tablet formulation is not effective against *Trichuris vulpis.* Dichlorvos has no activity against the migrating larvae of these worms. For more effective removal of *Trichuris vulpis,* the dog should be retreated in 10 to 14 days. In fact, it may be necessary to treat at intervals over a period of three months, due to the prepatent period of *Trichuris vulpis.*

Warning: Dichlorvos can be toxic, it should not be used with other cholinesterase-inhibiting chemicals, taeniacides, antifilarials, muscle relaxants, phenothiazine tranquilizers, or central nervous system depressants. Dichlorvos is contraindicated for dogs and cats showing signs of severe constipation, mechanical blockage of the intestinal tract, liver disease, or circulatory failure. Dogs with *D. immitis* infection should not be treated with dichlorvos. A small number of normal dogs may vomit after treatment but no other adverse reactions have been reported. Cats are more susceptible to dichlorvos toxicity. They may vomit, hypersalivate, appear apprehensive, and pass loose stools after medication. Atropine and pralidoxime (2-PAM) are the recommended antidotes for organophosphate poisoning.

Isoquinolones

The isoquinolones are represented by two closely related cestocides: praziquantel and epsiprantel. This class of cestocide is the safest and most effective yet approved in the United States. They attack the parasite neuromuscular junction and the tegument. These drugs cause increased cell membrane permeability to calcium and resulting loss of intracellular calcium. This effect produces an instantaneous contraction and paralysis of the parasite (Andrews et al., 1983). The second effect is a devastating vacuolization and destruction of the protective tegument (Vanden Bossche et al., 1985). The combined effects of paralysis and tegmental destruction provide excellent activity against cestodes.

Praziquantel

Praziquantel was the first isoquinolone cestocide approved in the United States; it displays marked anthelmintic activity against a wide range of adult and larval cestodes and trematodes of the genus *Schistosoma*. Oral administration results in nearly complete absorption and rapid distribution throughout the body and across the blood brain barrier. High tissue concentrations may be found in the liver and kidneys (USP, 1998). The half-life in dogs is 3 hours. The majority (80%) of the drug is eliminated through the kidneys and the remainder through the liver and bile.

Praziquantel is a very safe anthelmintic. Rats tolerated daily administration of up to 1000 mg/kg for 4 weeks, and dogs tolerated up to 180 mg/kg per day for 13 weeks. Vomiting is typically observed at high dosage rates. Injected doses of 200 mg/kg were lethal in cats. Praziquantel did not induce embryotoxicity, teratogenesis, mutagenesis, or carcinogenesis, nor did it affect the reproductive performance of test animals. Occasional adverse experiences in clinical use include anorexia, diarrhea, salivation, vomiting, and weakness. Overdoses have been reported to cause diarrhea, depression, incoordination, tremors, salivation, and vomiting.

Praziquantel (Droncit) is administered orally or injected subcutaneously at 2.5 to 7.5 mg/kg for the removal of *Dipylidium caninum, Taenia taeniaeformis, Taenia pisiformis, Taenia hydatigena, Mesocestoides corti, Echinococcus granulosus* and *Echinococcus multilocularis* (Andersen et al., 1978, 1979; Gemmell et al., 1977, 1980; Kruckenberg et al., 1981; Thakur et al., 1978; Thomas and Gonnert, 1979). Praziquantel is not intended for use in puppies or kittens less than 4 weeks old. Several combination products contain praziquantel; see the section on combination products for more information.

Epsiprantel

Epsiprantel (Cestex) was the second isoquinolone cestocide to be approved in the United States. Unlike its cousin praziquantel, epsiprantel is poorly absorbed after oral administration. Less than 0.1% is recovered from the urine; there are no known metabolites (Plumb, 1999). Because of the low bioavailability, systemic toxicity is very unlikely. In acute toxicity studies in mice and rats the oral minimum lethal dose of epsiprantel was shown to be more than 5000 mg/kg. Doses as high as 100 mg/kg and 200 mg/kg in cats and dogs were well tolerated. Epsiprantel was given concurrently with diethylcarbamazine, anti-inflammatory drugs, insecticides, and other anthelmintic drugs with no incompatibilities observed. The safety of use of epsiprantel in pregnant dogs and cats has not been determined, and it should not be used in puppies and kittens less than 7 weeks old.

Epsiprantel at an oral dosage level of 2.75 mg/kg for cats or 5.5 mg/kg for dogs, as a single oral film-coated tablet, effectively removes *Dipylidium caninum, Taenia taeniaeformis, Taenia pisiformis,* and *Taenia hydatigena* (Corwin et al., 1989; Manger and Brewer, 1989).

Arsenicals

Heavy metals like arsenic and antimony are well represented in the history of anthelmintics. Today they have been largely replaced by safer and more effective drugs for the most common parasites. Their use is now limited to removal of adult *D. immitis.* The therapeutic effect is dependent upon a reaction between the arsenic salt and sulfhydryl-containing enzymes (Hardman et al., 1996; Leadbetter, 1984). Inactivation of parasite enzyme systems then results in death. Arsenic is widely known as a toxin in man and animal, therefore due caution is required when using these products.

Thiacetarsamide

Thiacetarsamide (arsenamide sodium) is an organic arsenical that is available as a sterile one % buffered injectable solution (Caparsolate). It is administered intravenously for the treatment of adult *D. immitis* infection in dogs (Courtney et al., 1986; Otto and Maren, 1947). After intravenous administration, it is widely distributed in the body and concentrates in the liver and kidneys. The drug is metabolized and excreted in the bile and also in the urine. After 48 hours, 85% of the drug is excreted, mostly in the feces (66%). The elimination half-life is about 43 minutes and the clearance is approximately 200 mL/kg per hour (Plumb, 1999).

Due to the extensive metabolism and inherent toxicity of the drug, it should not be used, or used with extreme caution in animals with impaired hepatic, renal, or cardiopulmonary function. Similarly patients with diabetes mellitus, hypoadrenocorticism, or gastrointestinal disease should be watched closely while receiving thiacetarsamide therapy (Plumb, 1999).

Thiacetarsamide has no activity against heartworm microfilaria. The reported efficacy against adult heartworms has been reported to be 60% to 85%. The early fifth stage larvae and 2-year-old adult heartworms are the most susceptible to thiacetarsamide (Blair et al., 1983). Adolescent female worms are less susceptible than males. It is now clear that a refractory heartworm infection, an apparent drug failure, indicates the presence of maturing worms. Repeated thiacetarsamide therapy at intervals of a few months should eventually lead to complete elimination of the worms. Before treatment is initiated, a thorough health evaluation, including procedures required to assess liver, kidney, cardiovascular, and pulmonary function is recommended. The principal target organ for thiacetarsamide toxicity is the liver (Holmes et al., 1986; Winograd et al., 1992). Severe local reactions can also occur if the thiacetarsamide is injected extravascularly, including swelling and sloughing of the skin. The treated dog should have restricted activity to reduce the danger of massive pulmonary emboli from dying adult heartworms. The usual dose is 2.2 mg/kg twice a day for 2 days; higher doses have been reported but they appear to offer little increase in efficacy but significant increased risk of toxicity.

Melarsomine

Melarsomine dihydrochloride (Immiticide) is a trivalent arsenical with 92% to 98% efficacy against adult *D. immitis* (Dzimianski et al., 1992; Keister et al., 1992; Rawlings et al., 1993; Vezzoni et al., 1992). The arsenic content of the product is less than that of thiacestarsamide and is apparently less toxic to the patient. The product is administered intramuscularly at a dose of 2.5 mg/kg for two injections given 24 hours apart. Injections should only be made deep into the lumbar epaxial muscles along L3 to L5. Dogs that have significant illness from heartworms may be treated with an alternative regimen of a single injection followed by a rest period of 1 to 2 months, then given the standard two injections. This regimen is apparently less hazardous for the patient and results in higher percentage kill of the worms. Peak blood levels are achieved in 10.7 minutes after injection and the elimination half-life is 3 hours (USP, 1998). The toxic dose is 2.5 to 3 times the recommended dose and can result in panting, pulmonary inflammation, salivation, vomiting, edema, and death. Safety has not been determined in breeding, pregnant, or lactating dogs. Clinical studies indicate that the treatment is well tolerated even in dogs that have clinical signs of heartworm disease (Vezzoni et al., 1992). Adverse reactions in dogs include pain and swelling at the injection site, coughing, gagging, depression, lethargy, anorexia, fever, pulmonary congestion, and vomiting although they apparently occur in very low frequency and are self-limiting.

Miscellaneous Anthelmintics

The miscellaneous anthelmintics include a mixture of many different classes of drug, most are older chemicals that have not completely outlived their usefulness. Some have unique attributes that keep them in use and commercially available.

Dichlorophen

Dichlorophen (Happy Jack Tapeworm Tablets) is a chlorinated analogue of diphenylmethane. It has low toxicity for mammals. The oral LD_{50} for rats is 2690 mg/kg, and the acute oral LD_{50} in dogs is 1000 mg/kg. Dichlorophen has bacteriostatic, fungicidal, and cestocidal properties. It uncouples electron transport-linked phosphorylation in the parasite mitochondria; it is relatively safe in the host because of low gastrointestinal absorption (Lovell et al., 1990; Vanden Bossche et al., 1985).

Dichlorophen may be used either alone or in combination with other anthelmintic drugs for the removal of *Taenia* and *Dipylidium* tapeworms from dogs and cats (Roberson, 1988). The drug may be administered orally in tablet or capsule form at 220 mg/kg after an overnight fast. The tapeworms are killed, digested, and eliminated in an unrecognizable form. It is most commonly formulated with toluene in over-the-counter preparations; see the section on combination products for more information. An occasional animal may vomit or develop diarrhea after treatment with dichlorophen.

N-Butyl Chloride

Normal butyl chloride is commonly found in over-the-counter products (Happy Jack Worm Capsules, Sergeant's Sure Shot Capsules). It is administered orally to dogs and cats after an 18- to 24-hour fast at approximately 0.22 to 0.44 mL per kg of body weight up to a maximum of 5 mL (4.42 g) for the removal of *Toxocara canis, Toxocara cati,* and *Toxascaris leonina,* and as an aid (about 60% effective) in the control of *A. caninum, A. braziliense,* and *U. stenocephala.* The administration of *N*-butyl chloride should be followed in about 1 hour with a cathartic to maximize its anthelmintic effect. Dogs and cats can be fed their regular feed within 4 to 8 hours after treatment. Treatment may be repeated in 7 to 14 days. An occasional animal may vomit but no other untoward side effects have been reported (Courtney and Roberson, 1995).

Toluene

Toluene (methylbenzene) is a hydrocarbon derived from coal tar and is often used as an industrial solvent. It is surprisingly safe for mammals; the oral LD_{50} for rats is 7.5 mL/kg. Toluene is most commonly available in combination with dichlorophen in over-the-counter anthelmintics sold in grocery stores and pet shops.

Toluene orally at 0.22 mL/kg in dogs and cats is 98% effective for the removal of *Toxocara canis, Toxocara cati, Toxascaris leonina,* and 96% effective against *A. caninum,* and *A. braziliense* (Courtney and Roberson, 1995). The mechanism of action is postulated to be due either to irritant or to depressant effects on the neural cells of the nematode (Lovell et al., 1990). Fasting is suggested for 12 hours before and 4 hours after medication.

BROAD-SPECTRUM COMBINATIONS

The veterinary practitioner is always looking for anthelmintic products that cover ever increasing spectra of parasites. Broad-spectrum products have two important advantages. First they obviate dosing with several different products at once when a patient has a mixed parasite infection; this makes administration easier. Second, it provides peace of mind that a parasitized animal will be cleared of parasites that may have escaped detection. For instance a puppy from the animal shelter will be better served with a product that is effective in removing both roundworms and hookworms, than with a product that is only effective against roundworms.

There are two ways to get broad-spectrum products, either discover a single chemical that is broad spectrum (not an easy task) or combine several compatible active ingredients to build the spectrum of activity that is desired.

In this section the combination products are discussed. In some cases the formulation may have changed, and the dosing regimen is different than the single entity drugs discussed above. The toxicity and mechanism of action are also discussed above.

Dichlorophen Plus Toluene

A number of small animal proprietary anthelmintic products (Trivermicide Worm Caps, Vermiplex) contain dichlorophen as the cestocidal ingredient and toluene (methylbenzene) as the antinematodal ingredient. Both drugs have low mammalian toxicity.

The dichlorophen and toluene mixture is administered orally in soft capsules to dogs and cats, preferably after a 12 hour fast, at 220 mg dichlorophen and 264 mg (0.22 mL) toluene per kilogram of body weight for the removal of *Toxocara canis, Toxascaris leonina, A. caninum, Uncinaria stenocephala, Taenia pisiformis,* and *Dipylidium caninum.* The dichlorophen-toluene mixture is relatively ineffective against *Echinococcus granulosus* (Lovell et al., 1990).

Warning: Toluene is a relatively safe drug but overdosage produces ataxia, aberrant behavior, mydriasis, vomiting, depression, muscle tremors, and hypersalivation. Treatment should consist of general supportive care, including intravenous fluids, oxygen, administration of activated charcoal, and monitoring for possible renal or hepatic damage (Lovell et al., 1990). Treatment with digestible oils, alcohol, and adrenaline should be avoided.

Diethylcarbamazine Plus Oxibendazole

Filaribits Plus chewable tablets are formulated to deliver 6.6 mg diethylcarbamazine and 5 mg oxibendazole per kilogram of body weight. The medication is administered once a day for the prevention of infections with *D. immitis,* and *A. caninum,* and for the removal and control of *Toxocara canis,* and *Trichuris vulpis.* Filaribits Plus administration has been occasionally associated with hepatic dysfunction and several fatalities. Clinical signs reported as accompanying hepatic dysfunction include anorexia, vomiting, lethargy, jaundice, weight loss, polydipsia, polyuria, ataxia, and dark urine (Vaden et al., 1988). Exhaustive toxicologic evaluation by the manufacturer demonstrated that diethylcarbamazine and oxibendazole given individually each showed wide margins of safety. Dogs given a single dose of Filaribits Plus at 640 times the recommended dose level survived without any sequelae. Dogs given five times the recommended dose level daily for 2 years suffered no ill effects and at necropsy showed no drug-related histopathology (Simpson, 1986). Dickinson and Thornburg (1988) reported that analysis of a number of cases with hepatotoxic symptoms led them to the conclusion that Filaribits Plus is not an intrinsic hepatotoxin because the incidence of such reactions is low.

Febantel Plus Praziquantel

Febantel-praziquantel paste (RM Parasiticide-10) contains 34 mg of febantel and 3.4 mg of praziquantel per gram of paste. It is administered to dogs and cats over 6 months of age orally or in the food daily for 3 consecutive days at a dose level of 10 mg of febantel and 1 mg of praziquantel per kilogram of body weight. For puppies and kittens, the label recommends giving 1.5 times the adult dosage.

Dogs and Puppies Administration of febantel-praziquantel paste is used to remove *A. caninum, U. stenocephala, Trichuris vulpis, Toxocara canis, Toxascaris leonina, Dipylidium caninum,* and *Taenia pisiformis* (Andersen et al., 1985; Greiner et al., 1992; Sharp and McCurdy, 1985).

Cats and Kittens Febantel-praziquantel paste is effective in removing *A. tubaeforme, Toxocara cati, Dipylidium caninum,* and *Taenia taeniaeformis* (Corwin et al., 1984). It is suggested that febantel-praziquantel paste not be given to pregnant bitches and queens.

Febantel Plus Praziquantel Plus Pyrantel

A three-way combination of febantel, praziquantel, and pyrantel (Drontal Plus) is widely used outside the United States and is now approved by the FDA. This product is formulated to deliver at least 25 mg febantel, 5 mg praziquantel, and 5 mg pyrantel pamoate per kilogram. A single dose is given to dogs to remove *Dipylidium caninum, Taenia pisiformis, Echinococcus granulosus, Echinococcus multilocularis, A. caninum, U. stenocephala, Toxocara canis, Toxascaris leonina,* and *Trichuris vulpis* (Bowman and Arthur, 1993; Cruthers et al., 1993). It is interesting to note that this combination is effective against the nematodes when given in single dose while febantel alone requires three daily doses to be effective in monogastric animals. This combination should not be used in pregnant dogs, dogs under 2 pounds in body weight or puppies less than 3 weeks of age.

Pyrantel Plus Praziquantel

A two-way combination tablet containing pyrantel and praziquantel (Drontal) is now approved for use in the United States. This product is formulated to deliver a minimum dose of 20 mg/kg pyrantel pamoate and 5 mg/kg of praziquantel. A single dose is given to cats and kittens to remove *Dipylidium caninum, Taenia taeniaeformis, Ancylostoma tubaeforme,* and *Toxocara cati.* The product is 98% effective and well tolerated. Cats maintained in conditions of heavy or constant parasite exposure should be re-evaluated in 2 to 4 weeks.

Ivermectin Plus Pyrantel Pamoate

Ivermectin is available in combination with pyrantel pamoate in a beef-based chewable product (Heartgard Plus). The product is formulated to deliver a target dose of 0.006 mg ivermectin and 5 mg pyrantel pamoate per kilogram of body weight. The product is given orally to dogs every 30 days to prevent *D. immitis* and for the treatment and control of *Toxocara canis, Toxascaris leonina, A. caninum,* and *U.*

stenocephala (Clark et al., 1992a). The product should be given at monthly intervals during the heartworm season. Recent studies have shown that adult heartworms are not able to maintain detectable levels of microfilariae when exposed to ivermectin, so an antigen test should be used to reveal the presence of adult heartworms (Bowman et al., 1992). Safety tests have revealed that the ivermectin, pyrantel combination is well tolerated (Clark et al., 1992b).

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Anti-inflammatory Drugs

16

Dawn Merton Boothe

THE PATHOPHYSIOLOGY OF INFLAMMATION
The Role of Chemical Mediators in the Inflammatory Response
NONSTEROIDAL ANTI-INFLAMMATORY DRUGS
Chemistry
Mechanism of Action
Effects on Articular Cartilage
Pharmacokinetics
Pharmacologic Effects
Drug Interactions
Adverse Reactions
  Gastrointestinal
  Hematopoietic
  Renal
  Miscellaneous
Drugs
  Aspirin
  Carprofen
  Etodolac
  Meloxicam
  Phenylbutazone
  Flunixin Meglumine
  Ketoprofen
  Piroxicam
  Ketorolac
  Naproxen
  Ibuprofen
  Meclofenamic Acid
  Indomethacin
  Acetaminophen
Treatment of Osteoarthritis
  Osteoarthritis Defined
  Cartilage Physiology and Pathophysiology
  Drug Therapy
DISEASE-MODIFYING AGENTS: CHONDROPROTECTANTS
Injectable Products
  Polysulfated Glycosaminoglycans
  Pentosan Polysulfate
  Hyaluronic Acid
Oral Disease-Modifying Agents
  Veterinary Nutraceuticals
  Nutraceutical Disease-Modifying Agents
OTHER ANTI-INFLAMMATORY DRUGS
Orgotein
Dimethylsulfoxide
  Pharmacologic Effects
  Disposition
  Adverse Effects
  Clinical Use
  Methylsulfonylmethane
Pentoxifylline
MODULATORS OF INFLAMMATION IN THE TREATMENT OF SHOCK AND CENTRAL NERVOUS SYSTEM TRAUMA
Pathophysiology of Septic Shock
Role of Lipid Peroxidation in Tissue Injury
Drugs that Impair Lipid Mediators

THE PATHOPHYSIOLOGY OF INFLAMMATION

Inflammation can occur in any vascularized tissue in the body. The sequelae of inflammation are manifested as five cardinal signs: redness, heat, swelling or edema, pain, and loss of function. Vasoconstriction of small vessels in the area of injury is the initial vascular response to damage. Vascular occlusion serves to control hemorrhage. Within 5 to 10 minutes, however, vasodilation and increased vascular permeability of small venules occur. Leukocytes, platelets, and erythrocytes in the injured vessels become "sticky" and adhere to the endothelium. Leakage of cells and plasma-derived protein-rich fluid is followed by platelet aggregation and fibrin formation.

Initially, the predominant cell type infiltrating damaged tissues is the polymorphonuclear leukocyte (PMN), in part because it predominates in circulation. As the short-lived PMNs die, macrophages become the predominant cell type. The migration and concentration of PMNs to the site of injury is facilitated by chemical mediators that act as chemotactic agents. As PMNs die, the contents of the lysed cells accumulate to form the component of inflammatory exudate commonly referred to as *pus.*

THE ROLE OF CHEMICAL MEDIATORS IN THE INFLAMMATORY RESPONSE

The mediators released during the inflammatory process (Fig. 16–1) perpetuate the inflammatory response and are responsible for the clinical signs associated with inflammation, including pain and fever (Vane and Botting, 1987). Mediators of inflammation (Table 16–1) are derived from both the cells and fluid that reach the site of tissue damage from blood. Although quantitative differences between species and tissue concentrations of the mediators vary, the effect on and role in the pathophysiology of inflammation that each mediator has are predominantly the same.

Leukocytes are a rich source of a variety of chemical mediators of inflammation. These cells, as well as cells of other tissues that are injured and dying after either the initial damage or subsequent inflammation, perpetuate the inflammatory response. Mediators include lysosomal and other enzymes, granular mediators such as histamine and serotonin, eicosanoids or products of arachidonic acid (AA) metabolism (prostaglandins, leukotrienes, and related compounds), platelet-activating factor, oxygen radicals, and cytokines. The role each of these mediators has in the perpetuation of the inflammatory response varies, depending in part on the phase of inflammation during which the mediator is released.

Plasma-derived mediators are also important contributors to the inflammatory process. Examples include kinins (e.g., bradykinin), released from their precursor form after appropriate physiologic or pathologic stimulation; complement and complement-derived peptides, released after activation of either the classic or alternative pathway; and fibrinopeptides, released during the conversion of fibrinogen to fibrin during the clotting process and subsequent proteolysis of fibrin by plasmin.

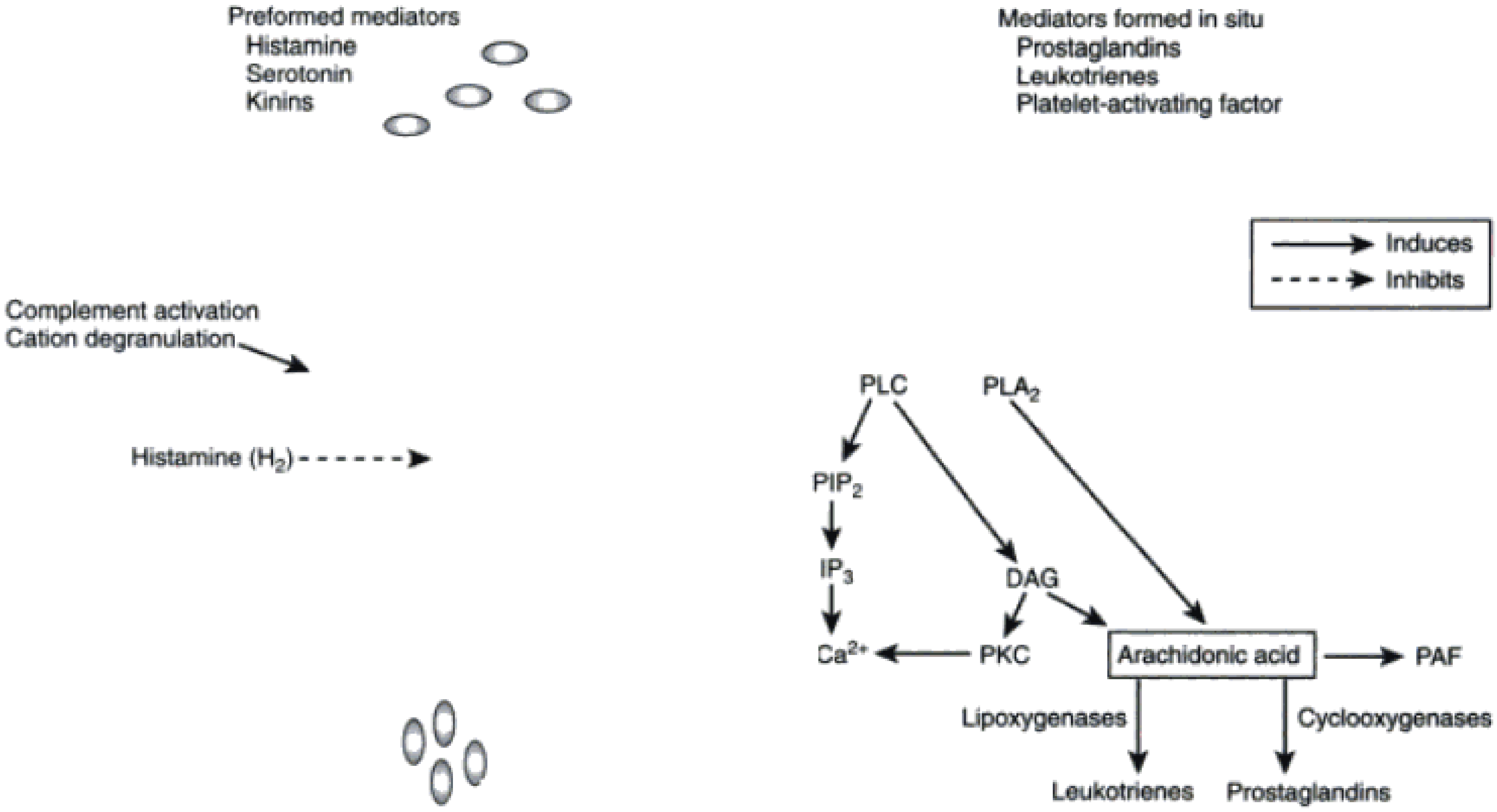

Figure 16–1. Leukocytes are an important source of inflammatory mediators that perpetuate the inflammatory response. Cellular mediators of inflammation include those preformed in granules or lysozomes, such as histamine and serotonin, and those formed in situ from arachidonic acid released by phospholipases in the cell membrane. Muscarinic receptors (M_3) stimulate, and β-adrenergic receptors (β_2) inhibit, inflammatory mediator release. Although the phagocytic cell is intimately involved in the inflammatory reaction, it is not the only cell type capable of generating mediators of inflammation. The mediators of cellular origin interact with plasma-derived mediators, further compounding the response. Drugs used to control inflammation target specific mediators (see Table 16–1). cAMP = cyclic adenosine monophosphate; cGMP = cyclic guanosine monophosphate; DAG = diacylglycerol; IP_3 = inositol triphosphate; PAF = platelet-activating factor; PDE = phosphodiesterase; PIP_2 = phosphatidylinositol; PLA_2 = phospholipase A_2; PLC = phospholipase C.

Acute inflammation can cause severe organ or life-threatening damage. Monocytes, which follow neutrophils to the site of inflammation several hours later, release collagenases and elastases, softening local tissues. Interleukin release draws fibroblasts to the area, which, in turn, deposit collagen at the site. The collagen is gradually remodeled and new blood vessels continue to form until oxygen tension is normal. If the cause of inflammation is removed, healing is complete. Failure to remove the inciting cause leads to persistent inflammation.

Pharmacologic control of inflammation is oriented toward preventing the release of various chemical or plasma mediators, inhibiting their actions, and treating pathophysiologic responses to them. Drugs useful for modulating the activity of chemical mediators derived from cells, plasma, or both are summarized in Table 16–1.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Chemistry

Although nonsteroidal anti-inflammatory drugs (NSAIDs) have been variably defined, the name is used to describe compounds that are not steroidal and that suppress inflammation (Table 16–2). Generally, the classification is restricted to those drugs that inhibit one or more steps in the metabolism of AA (Boynton et al., 1988). The NSAIDs vary in their ability to influence inflammation. The mechanism of action of some of these drugs is not limited to inhibition of AA metabolism (Hochberg, 1989).

Aspirin, one of the earliest components of herbal therapy, is the progenitor NSAID, and terms such as *aspirin-like* and *aspirin and related drugs* are commonly used to refer to NSAIDs (Boynton et al., 1988). Structurally, NSAIDs can be broadly classified as either the salicylate or carboxylic acid derivatives including the indoles (indomethacin), propionic acids (carprofen, ibuprofen, and naproxen), fenamates (mefenamic acid), oxicams (piroxicam), and pyrazolones or enolic acids (phenylbutazone and dipyrone) (Boynton et al., 1988).

Mechanism of Action

Eicosanoids, such as prostaglandins and leukotrienes, are 20-carbon-chain derivatives of cell membranes. Eicosanoids are potent mediators of inflammation and are particularly important in the later stages (Robinson, 1989a). These compounds are synthesized when oxygen reacts with the polyunsaturated fatty acids of cell membrane phospholipids (Figs. 16–1 and 16–2). The most important of these fatty acids is AA, which is released into the cell from phospholipids of the damaged cell membranes. Release reflects activation of phospholipase located in the cell membrane. Once inside the cell, AA serves as a substrate for enzymes that generate intermediate and ultimately the final eicosanoid end product (see Fig. 16–2) (Weissmann, 1991; Rob-

Table 16–1. Mediators Important in the Course of Inflammation

Mediator	Source	Action	Pharmacologic Modulator
Lysosomal contents	Phagocytes	Vessel permeability Membrane degradation Chemotactic factors Collagen, fibrin, cartilage, etc., degradation	Glucocorticoids Dimethylsulfoxide Organic gold compounds
Histamine	Granulocytes	Vasodilation Capillary permeability Pain	Antihistamines (particularly H_1, possibly H_2 blockers)
Serotonin	Platelets	Vasodilation/constriction Capillary permeability	
Eicosanoids Prostaglandins Leukotrienes Lipoxygenases	All cells	Chemotaxis Vascular permeability Vasodilation Pain	Glucocorticoids Nonsteroidal anti-inflammatories
Platelet-activating factor	Platelets	Platelet aggregation Chemotaxis Oxygen radical production	Glucocorticoids
Oxygen radicals	Damaged tissues Leukocytes	Highly destructive to number of cellular constituents, particularly lipid membranes	Superoxide dismutase Vitamin E Ascorbic acid Dimethylsulfoxide Xanthine oxidase inhibitors
Kinins	Plasma	Vasodilation Capillary permeability Pain	Nonsteroidal anti-inflammatories
Complement	Plasma	Lysis of cells Histamine release Vascular permeability Release of lysosomal contents Chemotaxis	Glucocorticoids Dimethylsulfoxide Antihistamine
Fibrinopeptides	Plasma	Enhance kinins Vascular permeability Chemotaxis	Nonsteroidal anti-inflammatories(?)

inson, 1989a). Cyclooxygenases (prostaglandin synthase or prostaglandin H [PGH] synthase), located in all cells except mature red blood cells, add oxygen to AA, generating unstable prostaglandin endoperoxides (PGG_2). Subsequent peroxidase reactions converts PGG_2 to PGH_2, the precursor of all prostaglandins and thromboxane. The final prostaglandin end product depends on the presence of specific isomerase reductase or synthetase enzymes (Robinson, 1989a).

The role of prostaglandins in normal physiology might best be understood by considering them as protective in nature. Their formation is mediated by one of two isoforms of cyclooxygenases (see Figure 16–2) located on different genes in people (Griswold and Adams, 1996; Williams, 1996; Crawford, 1997). Cyclooxygenase 1 (COX1), the "housekeeping" isoform (Crawford, 1997), mediates the formation of constitutive prostaglandins produced by many tissues, including gastrointestinal cells, platelets, endothelials cells, and renal cells. Prostaglandins generated from COX1 are constantly present, providing homeostasis through a variety of normal physiologic effects. These include protection of the gastrointestinal mucosa, hemostatsis, and the kidney when subjected to hypotensive insults. Cyclooxgenase 2 (COX2) is the product of an "immediate-early" gene that is rapidly inducible and tightly regulated (Crawford, 1997). Its expression is tightly restricted under basal conditions, but it is dramatically upregulated in the presence of inflammation. Proinflammatory cytokines such as tumor necrosis factor (TNF) and the interleukins stimulate the expression of COX2 in many cell types, such as synovial cells, endothelial cells, chondrocytes, osteoblasts, and monocytes and macrophages (Crawford, 1997). Cyclooxygenase 2 thus catalyzes the formation of inducible prostaglandins, which are needed only intermittently (Griswold and Adams, 1996; Williams, 1996; Cashman, 1996; Donnelly and Hawkey, 1997). Although the clinical relevance of the two forms of cyclooxygenase has yet to be elucidated, differential or selective inhibition of COX2 clearly offers potential benefits regarding safety by avoiding loss of homeostatic prostaglandins (Crawford, 1997). It is important to note that COX2 is constitutively expressed in the kidney and brain and mediates a cytoprotective effect in damaged or inflamed gastrointestinal mucosa.

Inflammation is mediated or perpetuated by prostaglandins by inducing vasodilation, changes in capillary permeability, and chemotaxis, all of which can be caused by inflammatory prostaglandins. Prostaglandin E is the predominant prostaglandin mediator of inflammation. Prostaglandins also potentiate the effects of other chemical mediators of inflammation, such as histamine and bradykinin, and are capable of inducing a state of hyperalgesia. Although specific points remain controversial, the role of prostaglandins in the inflammatory process have been described (Robinson, 1989a). Prostaglandin E (PGE) also modifies both T-cell and B-cell function, in part by inhibition of interleukin-2 (IL-2) secretion (Robinson, 1989a). Although all tissues have the capacity to produce cyclooxygenase end products, the concentration varies with the type and amount of the individual isomerase (Robinson, 1989a).

Nonsteroidal anti-inflammatory drugs act to block the first step of prostaglandin synthesis by binding to and inhibiting cyclooxygenase (Robinson, 1989a) (see Fig. 16–

Table 16–2. Doses of Nonsteroidal Anti-inflammatory Drugs in Cats and Dogs

Drugs	Dosages
Acetaminophen	
Dog	10–15 mg/kg 6–8 h PO
	20–30 mg/kg sustained release 8–12 h PO
Adequan	
Dog	5 mg/kg qod × 3/week for 5–6 weeks
Cat	2 mg/kg IM q3–7d
Aspirin	
Dogs	10 mg/kg q12–8 h PO
	10 mg/kg q24 h PO (endarteritis)
	10 mg/kg q12 h (antipyresis)
	25–35 mg/kg q8 h
	25 mg/kg q12 h PO (autoimmune diseases)
	25–35 mg/kg q24 h PO (preoperative ocular surgery)
	40 mg/kg q18h (anti-inflammatory)
	3 mg/kg q6d (antithrombotic)
Cats	10 mg/kg 48 h PO
	10 mg/kg 24 h (antithrombotic)
	15 mg/kg 24 h (anti-inflammatory)
	10 mg/kg 12 h (antipyresis and analgesia)
	25–42 mg/kg 24 h (anti-inflammatory)
	25–35 mg/kg 8 h (anti-inflammatory)
	75 mg/kg 48 h (antithrombotic)
Dipyrone	
Dog	25 mg/kg IM, SC q8–12h
Cat	10–25 mg/kg IM, SC q24h
Etodolac	
Dog	10–15 mg/kg PO q24h*
Flunixin meglumine	
Dogs	0.5–1 mg/kg q24 h IV, IM × 1–3 (analgesic)
	0.25 mg/kg IV q24 h × 5 (uveitis)
Ibuprofen	
Dog	10 mg/kg PO q24–48h (strongly recommended not to be used)
Ketoprofen	
Dog	0.5–2.2 mg/kg PO q12h
Cat	2.2 mg/kg initial dose followed by 1 mg/kg qod
Ketorolac	
Dog	0.3–0.5 mg/kg IV, IM q8–12h × 2
Cat	0.25 mg/kg IM q8–12h
Meclofenamic acid	
Dog	1.1–2.2 mg/kg PO q24h
Meloxicam	
Dog	0.2 mg/kg followed by 0.1 mg/kg PO q24h
Naproxen	
Dogs	1–2 mg/kg PO q24–72 h
Pentosan polysulfate	
Dogs	3 mg/kg IM q7 days
Phenylbutazone	
Dog	10 mg/kg q8–12 h PO
	10–15 mg/kg q12 h IV (not to exceed 4 doses)
	22 mg/kg (not to exceed 800 mg) 8 h PO
Piroxicam	
Dog	0.3 mg/kg q48h
Hyaluronic acid	
Dog	20 mg/kg IV as needed (Campos, 1998)

Abbreviations: IM = intramuscular; IV = intravenous; PO = oral; qod = every other day; SC = subcutaneous.

*Dogs weighing less than 5 kg cannot be accurately dosed.

2). This action is both dose and drug dependent. The precise site at which cyclooxygenase is inhibited is not known. The planar form that characterizes these drugs is thought to facilitate their binding to cyclooxygenase (Boynton et al., 1988; Higgins, 1985). Several investigators have shown that some drugs (e.g., phenylbutazone and flunixin meglumine) also reduce formation of PGE_2 in inflammatory exudate at therapeutic doses (Lees et al., 1986). The major therapeutic and toxic effects of NSAIDs have been correlated extensively with their ability to inhibit prostaglandin synthesis (Robinson, 1989a). Their potency as anti-inflammatory agents relates to their relative potency of inhibition of prostaglandin synthesis (Robinson, 1989a).

The differential effect of NSAIDs on the isoforms of cyclooxygenase offers some insight into the differential pharmacologic and toxic effects of NSAIDs, particularly in the gastrointestinal tract (Laudanno and Cesolari, 1998). As a class, NSAIDs appear to inhibit both COX1 and COX2. The amount of drug necessary to inhibit each of the two isoforms, however, provides a basis for assessing the relative safety and efficacy of each drug. A number of in vitro studies have investigated the differential effect of NSAIDs on the two isoforms. The ratio of COX1 to COX2 describes the amount of drug necessary to inhibit the respective isoform of the cyclooxygenase enzyme. A drug that inhibits COX2 at a lower concentration than the concentration necessary to inhibit COX1 is probably safer because COX2 prostaglandins (inducible) are more likely than COX1 (constitutive) prostaglandins to be inhibited at concentrations studied. However, there is the problem of "selectivity" (or "relative selectivity"): inhibition of both COX2 and COX1 may occur at concentrations achieved therapeutically. A COX1 to COX2 ratio greater than 1 (or a COX2:COX1 ratio of less than 1) is desirable (Griswold and Adams, 1996; Williams, 1996; Cashman, 1996; Donnelly and Hawkey, 1997). Caution is recommended when applying the results of studies focusing on NSAID selectivity to clinical patients. Concentration differences between in vitro studies and those achieved therapeutically may eradicate selectivity. Species differences are just as important. For example, in studies using human cells, the COX1:COX2 ratio of etodolac is much more favorable than that for carprofen (Kawai et al., 1998; Warren et al., 1999), an observation that is supported clinically in humans using the drugs.

Ricketts and coworkers (1998) have studied the selectivities of various NSAIDs toward COX1 and COX2 using canine platelets and endotoxin-stimulated macrophage-like cells. The COX1:COX2 ratios for the NSAIDs studied were aspirin, less than 0.343; carprofen, 129 for the racemic mixture, 181 for the S isomer, and more than 4.19 for the R isomer; etodolac, 0.517; flunixin meglumine, 0.635; ketoprofen, 0.232; meclofenamic acid, 15.4; meloxicam, 2.90; nimesulide, 38; phenylbutazone, more than 2.64; and tolfenamic acid, 15.0. Species differences exist in relative sensitivity of COX1 versus COX2 among the NSAIDs (Ricketts et al., 1998), and the relative safety of an NSAID for one species should not be interpreted as safety for others. Clinical response to these drugs should guide the relevancy of COX1:COX2 ratios.

Lipoxygenase enzymes located within cells can also metabolize AA to inflammatory mediators (Hochberg, 1989; Newcombe, 1988). Among these enzymes, 5-lipoxygenase appears to be the most important (Robinson, 1989a). This enzyme adds oxygen to AA to form 5-hydroperoxyeicosatetraenoic acid (HPETE). Leukotriene (LT) C4, LTD4, and LTE4 result from addition of glutathione on LTA4 by glutathione S transferase. Each of these is a potent mediator of inflammation. In addition, LTA4 can

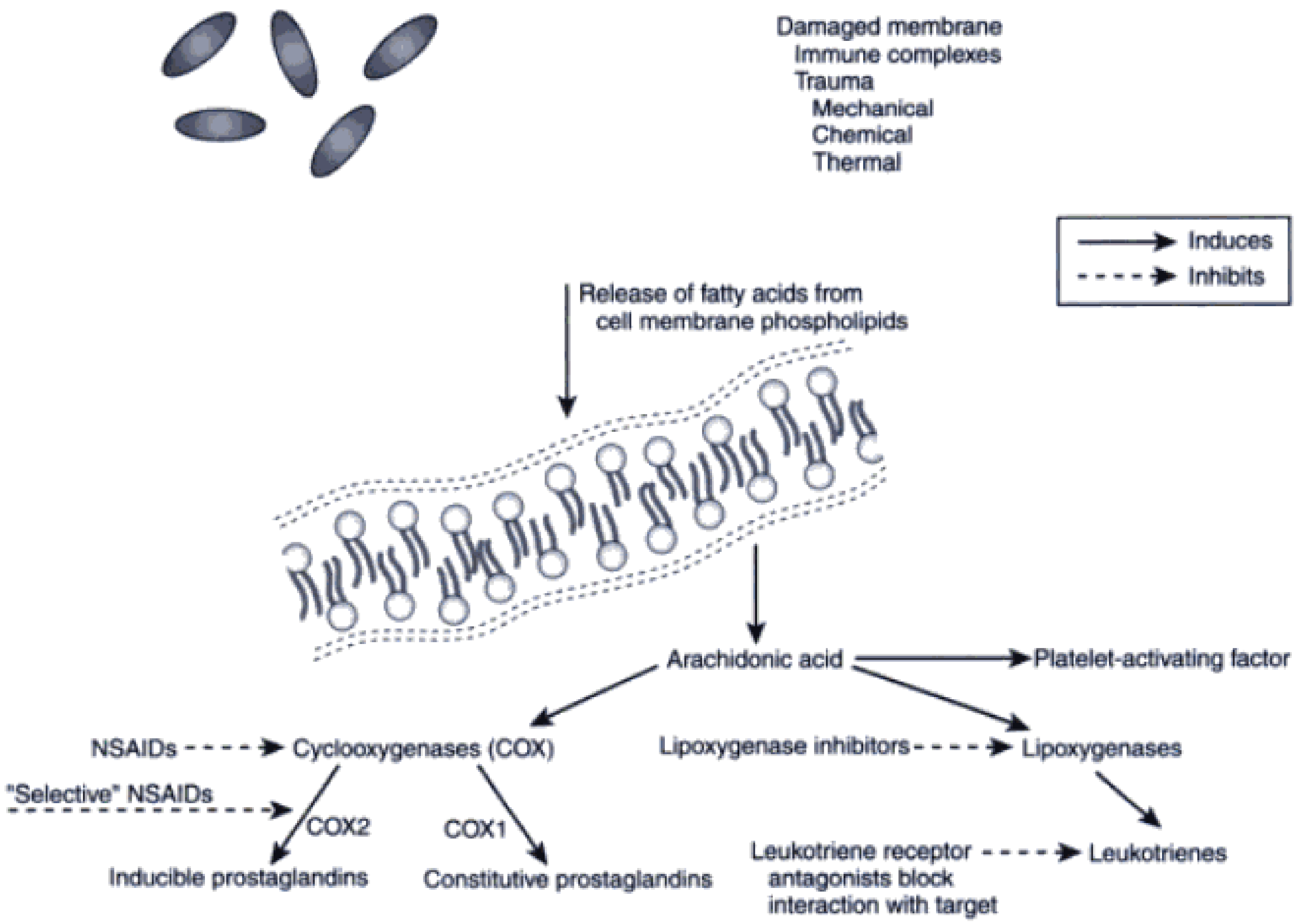

Figure 16–2. The release of arachidonic acid from the phospholipids in cell membranes leads to a cascade of events resulting in the formation of inflammatory mediators. The family of cyclooxygenases (COX) results in the formation of constitutive prostaglandins (COX1) and inducible prostaglandins (COX2). The inducible prostaglandins contribute to all cardinal signs of inflammation. Selectivity of NSAIDs for COX2 ultimately may result in marked safety of the nonsteroidal anti-inflammatory drugs (NSAIDs). Lipoxygenases result in the formation of leukotrienes, which, along with their precursors, are potent inflammagens in a number of tissues. Platelet-activating factor also is a potent inflammagen, although some of its actions may be mediated through leukotriene activity.

also be converted to LTB4, a potent chemotactic agent (Robinson, 1989a). Leukotrienes and other selected lipoxygenase products modulate lymphocyte function (Robinson, 1989a).

Lipoxygenases are not as ubiquitous as prostaglandins and are found predominantly in lungs, white blood cells, platelets, and the liver. Although their formation is restricted primarily to leukocytes, leukotrienes, and lipoxins, which are the end products of lipoxygenase activity, they are also potent mediators of local inflammation (Hochberg, 1989). Originally, studies indicated that NSAIDs were not capable of inhibiting leukotriene synthesis. A potential sequelae of cyclooxygenase blockade by NSAIDs is increased production of leukotrienes from AA that would have otherwise been metabolized to prostaglandin products (Robinson, 1989a). Aspirin hypersensitivity is associated with the diversion of AA from the prostaglandin to the leukotriene (5-lipoxygenase) pathway and the production of mediators that are more inflammatory than the products of PGH synthetase (Weissmann, 1991). Thus, NSAIDs may cause undesirable, unexpected effects by augmenting leukotriene synthesis (Robinson, 1989a). The anti-inflammatory efficacy of some of the NSAIDs (e.g., ketoprofen) (Daffonchio et al., 1996) has also been ascribed to inhibition of lipoxygenases and thus prevention of leukotriene formation (Boynton et al., 1988), although their ability to inhibit 5-lipoxygenase is controversial (Robinson, 1989a).

Inhibition of cyclooxygenase as the sole anti-inflammatory mechanism of action of NSAIDs has been scrutinized and criticized. The NSAIDs also appear to alter cellular and humoral immune responses and may suppress inflammatory mediators other than prostaglandins (Hochberg, 1989). Connective tissue metabolism may also be affected (Hochberg, 1989). As a group, all NSAIDs are planar and anionic and are able to partition into lipid environments, including neutrophil cell membranes. As a result, cell membrane viscosity is altered, even at low concentrations (Weissmann, 1991). At higher concentrations, NSAIDs appear to uncouple protein-protein interactions within the plasma membrane and thus interfere with a variety of cell membrane processes such as oxidative phosphorylation and cellular adhesion (Weissmann, 1991). The drugs appear to disrupt the response of inflammatory cells to extracellular signals by affecting signal transduction proteins (G proteins) (Weissmann, 1991). Thus, at low doses, PGH synthase appears to be the target of NSAIDs, whereas membrane-bound signal processing complexes appear to be the target at higher doses (Weissmann, 1991).

Studies using in vitro systems have shown that NSAIDs alter the inflammatory response by inhibiting activation of neutrophils and thus the subsequent release of inflammatory cellular enzymes such as collagenase, elastase, hyaluronidase, and others (Hochberg, 1989). Nonsteroidal anti-inflammatories interfere with multiple aspects of neutrophil function, including adherence. Some NSAIDs inhibit several neutrophil functions, whereas others inhibit few. The extent of inhibited neutrophil activation varies with the individual drug. For example, piroxicam inhibits both the generation of superoxide ions and the release of lysosomal enzymes, whereas ibuprofen does neither (Weissmann, 1991). All NSAIDs appear to inhibit neutrophil adhesion. Several NSAIDs, however, including phenylbutazone, oxyphenylbutazone, and flunixin, inhibit leukocyte cell movement. Of these drugs, flunixin is the most potent inhibitor in vitro at concentrations achieved in equine plasma and inflammatory exudate (Dawson and Sedgwick, 1987).

Nonsteroidal anti-inflammatory drugs are also capable of immunomodulation. Several prostaglandins and leukotrienes are important immunomodulators (Robinson, 1989a). Nonsteroidal anti-inflammatory cells indirectly influence lymphocyte activity through altered prostaglandin formation (Hochberg, 1989). Selected NSAIDs appear to enhance cellular immunity by inhibiting PGE_2, a mediator that dampens the immune response (Hochberg, 1989). This effect appears to be more important in the immunosuppressed animal.

NSAIDs are currently being investigated for their potential antitumor effects. Knapp and coworkers (1994) found piroxicam to be clinically useful in the reduction of tumor size and longer survival time in dogs with transitional cell tumors of the urinary bladder. The result does not appear to reflect direct cytotoxic effects (Knapp et al., 1992, 1994, 1995). NSAIDs may be beneficial when combined with other anticancer drugs (Braun et al., 1987).

Finally, central analgesic effects have also been suggested for some but not all NSAIDs because NSAIDs can provide analgesia at very low intrathecal doses (Laird et al., 1997; Cashman, 1996; Donnelly and Hawkey, 1997).

Effects on Articular Cartilage

Nonsteroidal anti-inflammatory drugs have been shown to inhibit proteoglycan synthesis in vitro, and for the salicylates this is supported by in vivo studies (Brandt, 1991). This effect has been attributed to inhibition of UDP-glucose dehydrogenase, an enzyme important in proteoglycan synthesis (Brandt, 1991). Hyaluronic acid synthesis, however, which also depends on this enzyme, does not appear to be as affected. The effects of NSAIDs on cartilage are controversial. More recent evidence indicates that some may, in fact, favorably modify the metabolism of proteoglycans, collagen, and matrix and may decrease the release of proteases or toxic oxygen metabolites (Brandt, 1991). Several NSAIDs have documented adverse effects on normal cartilage, ranging from decreased proteoglycan synthesis (e.g., aspirin) to chondrocyte death (phenylbutazone). Other drugs (e.g., naproxen, piroxicam, ketoprofen, and possibly carprofen) are recognized for their chondroprotective effects: they not only do not contribute to the degenerative process but they also appear to protect the joint from some of the degenerative processes. The effect of many NSAIDs (e.g., meclofenamic acid, flunixin meglumine) on cartilage apparently have not been determined.

Pharmacokinetics

The NSAIDs share a number of pharmacokinetic properties. As weak acids, the NSAIDs tend to be well absorbed after oral administration. Bioavailability can vary between animals but has not been established for many drugs because of the lack of intravenous (IV) preparations (Brater, 1988). Food can impair the oral absorption of some NSAIDs or contribute to drug interactions (Tobin et al., 1986; Munsiff et al., 1988). Solutions of selected injectable preparations tend to be alkaline and can cause necrosis or pain if perivascular leakage occurs. The drugs are lipid soluble but are characterized by a small volume of distribution (approximating 10%) due to binding to serum albumin that can exceed 90% (Galbraith and McKellar, 1996). Unbound drug is distributed to extracellular fluid. Only a small portion of pharmacologically active drug reaches peripheral tissues. Displacement from albumin due to competition with other substrates for binding sites or due to decreased serum albumin concentrations initially can result in higher than expected concentrations of pharmacologically active drug and thus predispose the patient to drug-induced adverse effects. Although this increase is transient due to increased clearance of unbound drug (Brater, 1988), it nonetheless can result in life-threatening side effects before clearance changes compensate for increased drug concentrations.

Clearance of the NSAIDs is variable, differing in rate and extent among drugs and species. Differences in clearance rates are largely responsible for differences in drug half-life among animals (Brater, 1988). Most are eliminated primarily by hepatic metabolism. Both phase I and phase II hepatic drug-metabolizing enzymes are important to elimination. Conjugated metabolites are predominantly eliminated through the urine, although several drugs undergo extensive enterohepatic circulation in some species (e.g., naproxen and meclofenamic acid in dogs) (Aitken and Sanford, 1975). For some drugs, a portion may be eliminated unchanged in the kidneys by active tubular secretion. Age and species differences in drug clearance should lead to caution when extrapolating doses from one animal to another. Although most pharmacokinetic studies measure total rather than unbound drug, clearance of unbound drug is substantially less in geriatric patients, whereas clearance of bound drug does not differ. The volume of distribution of unbound drug in adult animals is half that in pediatric patients. Because of these differences in NSAID disposition, geriatric and pediatric patients may require much smaller doses of the NSAIDS (Brater, 1988). Species differences in the elimination of the NSAIDs have been well documented and are responsible for some of the adverse reactions commonly associated with the use of these drugs. Stereoselective metabolism has also become an additional important consideration when extrapolating doses in human beings (Brater, 1988), and may become relevant when considering disposition in animals (see previous discussion of COX2-selective drugs).

Pharmacologic Effects

The pharmacologic effects of this class of drugs include analgesia, antipyresis, and control of inflammation. The mechanisms by which NSAIDs inhibit (interact with) cyclooxygenase are responsible, in part, for the variable anti-inflammatory effects that characterize these drugs. Aspirin binds reversibly to the cyclooxygenase activity site on PGH synthase and then inactivates the enzyme irreversibly by acetylating a serine residue (Weissmann, 1991). In platelets, the effects of aspirin on platelet activity remain for the duration of platelet life span because the platelet apparently cannot produce additional thromboxane synthetase enzyme. In contrast, endothelial cells are able to synthesize more prostacyclin synthetase and are less susceptible to the inhibitory effects of low doses of aspirin (Weissmann, 1991). In contrast to irreversible binders of cyclooxygenase, ibuprofen binds reversibly with cyclooxygenase and thus competes with AA. In laboratory animals and humans, a relative potency has been established for the NSAIDs: meclofenamic acid > indomethacin > naproxen > phenylbutazone > aspirin (Lee and Higgins, 1985). A similar pattern occurs in domestic animals: The relative potency of the NSAIDs in horses has been reported to be flunixin meglumine > meclofenamic acid > phenylbutazone > naproxen > aspirin (Lee and Higgins, 1985). Potency does not necessarily, however, confer a therapeutic advantage of one NSAID over another. Rather, each of these compounds may become equally effective simply by having its dose appropriately adjusted. Differences in COX1 versus COX2 selectivity (as previously discussed) also impact variable effects among the NSAIDs.

Along with inhibition of prostaglandins, disruption of cellular signaling is responsible for all three pharmacologic effects that characterize all NSAIDs. These effects also are dose- and drug-dependent and include antithrombosis, occurring at the lowest doses; analgesia and antipyresis; and anti-inflammation, which occurs at the highest doses (Weissmann, 1991). Although several NSAIDs are characterized by a short plasma elimination half-life, the clinical response may last for over 24 hours after a single dose or up to 72 hours after multiple doses. Irreversible binding to cyclooxygenase has been postulated as an explanation for the discrepancy between plasma half-life and biologic response (Lee and Higgins, 1985). Alternatively, prolonged elimination of NSAIDs from inflammatory exudate compared with plasma has also been suggested (Lee and Higgins, 1985; Tobin et al., 1986).

Drug Interactions

The NSAIDs can be involved in a variety of drug interactions during any phase of drug disposition. Displacement of only a small percentage of bound drug from albumin can increased the concentration of pharmacologically active drug in tissues. Few, if any, adverse reactions resulting from drug displacement have been reported, in part because of the failure to recognize the combination as problematic. In addition, the increase in pharmacologically active drug is only transient: clearance of the unbound drug by both the liver and kidneys will increase (Brater, 1988). Several NSAIDs can induce or inhibit drug-metabolizing enzymes and thus the clearance and half-life of other drugs cleared by the liver (Brater, 1988). Phenylbutazone can both increase and inhibit selected drug-metabolizing enzymes depending on the second drug, whereas salicylates increase metabolism (Brater, 1988). Renal competition with other organic acids for active renal tubular secretion in the proximal tubule has been documented for aspirin and other drugs, although the clinical relevancy of this is not clear.

Adverse Reactions

All NSAIDs induce undesirable and potentially life-threatening side effects. The most commonly consumed NSAIDs in accidental poisoning include ibuprofen, acetaminophen, aspirin, and indomethacin (Jonnes et al., 1992). The most common clinical signs of toxicosis in one study were vomiting, diarrhea, central nervous system (CNS) depression, and circulatory manifestations (Jonnes et al., 1992). Most adverse reactions reflect the inhibitory effects of NSAIDs on prostaglandin activity with manifestations most often being gastrointestinal in nature. In addition, acute intoxication by several drugs can be fatal.

Gastrointestinal

Gastrointestinal damage is the most common and serious side effect of the NSAIDs. Dogs appear to be very sensitive to the gastrointestinal side effects of these drugs; indeed, every NSAID recommended for use in dogs has been reported to cause gastrointestinal upset in dogs (Table 16–3). Although how the damage occurs is not completely understood, several mechanisms have been hypothesized (Figs. 16–3 and 16–4) (McCormack and Brune, 1987). Gastroduodenal erosion and ulceration reflect inhibition of COX1-stimulated PGE_2-mediated bicarbonate and mucous secretion, epithelialization, and increased blood flow (Chastain, 1987; Silverstein, 1998). Control of gastric acid secretion is consequently decreased, as is mucous and bicarbonate secretion, epithelialization of the mucosa, and mucosal blood flow. Breakdown of small blood vessels due to a deficiency of mucus may be the initiating lesion (Mazué et al., 1983). Direct irritation by acidic drugs may be important (Chastain, 1987). In addition, salicylates cause local damage due to "backdiffusion" of acid, which causes injury to mucosal cells and submucosal capillaries. Impaired platelet activity may contribute to mucosal damage.

There appears to be no chemical characteristic that predicts the likelihood of gastrointestinal toxicity by a particular nonselective NSAID (Chastain, 1987; Mazué et al.,

Table 16–3. Nonsteroidal-Induced Gastrointestinal Ulceration Reported in Dogs

Drug	Dose (mg/kg)	Interval (hours)
Aspirin	15	12
Carprofen	2.2	12
Etodolac	15	24
Flunixin meglumine		
Ibuprofen	8	24
Ketoprofen	0.5–1	12
Meclofenamic acid	0.5	8–12
Piroxicam	1	24
Phenylbutazone		

*Dose and interval are those at which gastrointestinal ulceration developed.

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Figure 16–3. An endoscopic view of a gastric ulcer in a dog treated with aspirin and glucocorticoids. The ulcer responded to treatment with misoprostol, sucralfate, and ranitidine.

1983). Drugs that enter the enterohepatic circulation (e.g., naproxen) may be associated with a greater incidence of gastrointestinal upset. Dogs are described as a species that is "exquisitively sensitive" (see package insert for meclofenamic acid, Fort Dodge) to NSAID-induced gastrointestinal ulceration. All NSAIDs used in the dog have been cited either in published reports or by word of mouth (Ellison, 1995; Shaw et al., 1997; Dye, 1997; Giannoukas et al., 1996; Vonderhaar and Salisbury, 1993; Matthews et al., 1996) to cause gastrointestinal ulceration. This includes relatively COX2-selective drugs, although they appear to be much safer than nonselective drugs. Gastrointestinal ulceration should be anticipated in dogs receiving these drugs and clients counseled regarding the side effects and potential treatments for ulcerative injury. Unfortunately, there is no sensitive indicator of gastrointestinal bleeding in dogs, and damage may be quite extensive before signs are evident (Boulay et al., 1986b). A method based on sucrose absorption in the gastrointestinal tract may ultimately be useful for detecting NSAID-induced gastrointestinal damage (Meddings et al., 1995).

Treatment for gastrointestinal toxicity should be to replace the missing prostaglandins, protect the damaged mucosa, and control gastric acid secretion (Collins and Tyler, 1985; Giannoukas et al., 1996). Misoprostol is a synthetic prostaglandin PGE analogue that both prevents and helps heal gastrointestinal ulceration caused by NSAIDs (Bowersox and Lipowitz, 1995). The efficacy of misoprostol has been well established in human patients suffering from NSAID-induced ulceration (Silverstein, 1998), and studies support similar benefits in dogs (Murtaugh et al., 1993; Johnston et al., 1995). Combination NSAID-misoprostol products have been approved for use by human patients (Shield, 1998), suggesting that a similar combination should be considered for dogs for whom the risk of NSAID-induced toxicity is increased due to age, increased dose, or other factors.

Interestingly, misoprostol when combined with an NSAID also appears to enhance the anti-inflammatory effect of the NSAID (Shield, 1998). Indeed, misoprostol inhibits IL-1, TNF, and thromboxane release from macrophages, and it is the most potent inhibitor of histamine release from human mast cells (Shield, 1998). Misoprostol has potentiated the anti-inflammatory effect of a variety of compounds in animals. Additionally, it appears to have analgesic effects, although at high concentrations, and to act synergistically with other NSAIDs in causing analgesia (Shield, 1998).

The benefits of sucralfate include binding to and thus protecting damaged mucosa, as well as increasing prostaglandin synthesis, angiogenesis, and sulfhydryl (oxygen radical scavenger) production at the site of damage. Antisecretory drugs such as ranitidine or other H_2-receptor antagonists or the proton pump blocker omeprazole can also be used, and are indicated for severe ulceration that does not respond to other therapy. However, by themselves, they may not be sufficient (Boulay et al., 1986a). Although perhaps more cost effective than misoprostol in their control of acid secretion, they do not replace the other cytoprotective effects of prostaglandins. Omeprazole may be preferred to H_2-receptor antagonists as an antisecretory drug. Note that misoprostol may be more effective in the presence of agents that decrease gastric acid secretion (Giannoukas et al., 1996).

Hematopoietic

All NSAIDs are able to impair platelet activity due to impaired prostaglandin (thromboxane) synthesis, a COX1 selective action (Fig. 16–5). At pharmacologic doses, aspirin selectively and irreversibly acetylates a serine residue of a platelet cyclooxygenase (Jackson, 1987). The platelet form of this enzyme is up to 250-fold more sensitive to acetylation by aspirin compared with cyclooxygenases (prostacyclin synthetase) in vascular endothelial cells. Although platelets cannot regenerate more cyclooxygenase, endothelial cells apparently are able to rapidly synthesize and replace impaired cyclooxygenase (Jackson, 1987). Platelet aggregation defects caused by aspirin can last up to 1 week. In addition to their antiplatelet effects, selected NSAIDs (e.g., phenylbutazone) have also been associated with bone marrow dyscrasias (Martin et al., 1984; Carlisle et al., 1968; Watson et al., 1980; Markel, 1986). Gastrointestinal bleeding is probably the most common sign of bleeding dyscrasias in part because of the ulcerogenic properties of these drugs. Epistaxis has also been reported. Because prostacyclin is mediated largely by COX2, use of COX2 selective drugs may increase the risk of thrombosis (Wallau, 1999).

Renal

Analgesic nephropathy is a relatively common adverse effect of NSAIDs in human beings (Dunn et al., 1988). It does not occur as frequently in domestic animals, however, in part because the drugs are not used as chronically. In the kidney, vasodilatory and tubuloactive prostaglandins are protective, ensuring that medullary vasodilation and urinary output continue during states of renal arterial vasoconstriction (Fig. 16–6). Both COX1 and COX2 mediate renal effects of prostaglandins. The loss of this protective effect becomes important in patients with compromised renal function (Dunn et al., 1988). Patients that are predisposed to analgesic nephropathy include geriatric patients, patients suffering from cardiac, renal, or liver disease, patients in hypovolemic states including shock and dehydration, and patients receiving nephrotoxic (e.g., aminoglycosides, amphotericin B, or other antiprostaglandin drugs) or nephroactive (e.g., diuretic) drugs.

Figure 16–4. Among the many protective functions of constitutive prostaglandins is protection of the gastrointestinal mucosa from acid and other mediator-induced damage. Protective mechanisms include production of mucus and bicarbonate and inhibition of hydrogen ion secretion; epithelial turnover, ensuring rapid replacement of damaged cells; and increased mucosal blood flow, ensuring provision of oxygen and nutrients to the rapidly dividing epithelial cells as well as removal of hydrogen ions that are able to pass into the cells.

Miscellaneous

Miscellaneous side effects associated with the use of NSAIDs include hepatotoxicity (Lewis, 1984), aseptic meningitis (Clemmons and Meyers, 1984; Berliner et al., 1985; Syvlia et al. 1988), diarrhea, and CNS depression (Jonnes et al., 1992).

Drugs

Aspirin: The Prototypic NSAID

Aspirin, the salicylic acid ester of acetic acid, is the prototype of the salicylate drugs, which include sodium salicylate, bismuth subsalicylate, and others. In addition to inhibition of cyclooxygenase enzyme activity, salicylates inhibit the formation and release of kinins, stabilize lysosomes, and remove energy necessary for inflammation by uncoupling oxidative phosphorylation. Aspirin is available in several different preparations, including plain, film coated, buffered, time-release, and enteric-coated tablets. Capsules and suppositories are also available (Chastain, 1987).

The oral bioavailability of aspirin products may vary due to differences in disintegration, drug formulation, stomach content, and gastric pH (Conlon, 1988). Although buffered aspirin is more soluble than plain aspirin, a larger proportion is ionized and less rapidly absorbed. The rate of absorption of both products is the same (Chastain, 1987). Aspirin undergoes rapid metabolism to the hydrolyzed active product salicylic acid. This metabolite is not as potent an analgesic or anti-inflammatory drug because of the loss of the acetyl group, which is able to acetylate key proteins (Chastain, 1987). Salicylic acid is between 50 and 70% bound to serum albumin among species (Davis and Westfall, 1972). Hypoalbuminemia may result in transient increases in plasma drug concentrations associated with adverse effects. Distribution of salicylic acid into extracellular fluid is rapid and includes synovial and peritoneal fluids, saliva, and milk. Salicylic acid is eliminated by hepatic conjugation with glucuronide and glycine, renal excretion by glomerular filtration, and tubular secretion (Davis and Westfall, 1972; Short et al., 1990). Species differences in the biotransformation and elimination of salicylate are

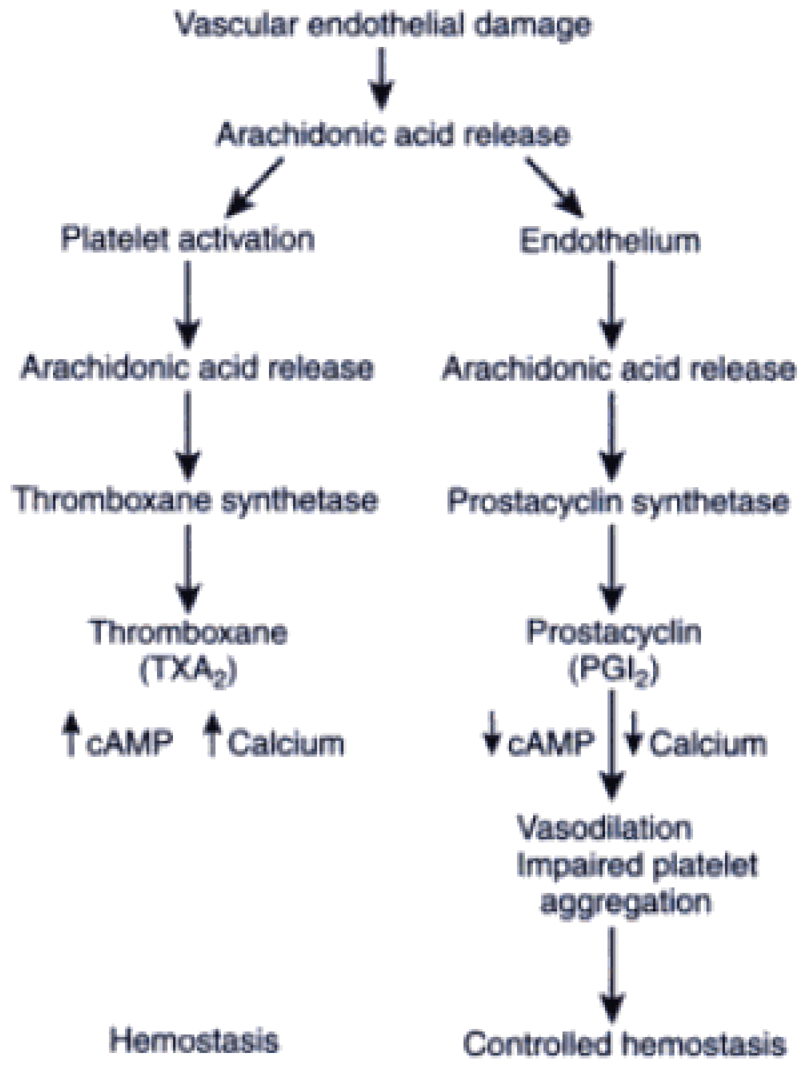


Figure 16–5. The role of constitutive prostaglandin products in hemostasis exemplifies the "yin-yang" relationship that often characterizes their action. Platelet activation in response to the damage is accompanied by the release of arachidonic acid, which is catalyzed by thromboxane synthetase, present in platelets, to thromboxane. Thromboxane causes platelet aggregation and local vasoconstriction. Excessive hemostasis is kept in check, however, by the simultaneous release of arachidonic acid from the damaged endothelial cell surface. Prostacyclin synthetase, located in the endothelial cells, results in the formation of prostacyclin, which is vasodilatory and inhibits platelet aggregation. cAMP = cyclic adenosine monophosphate.

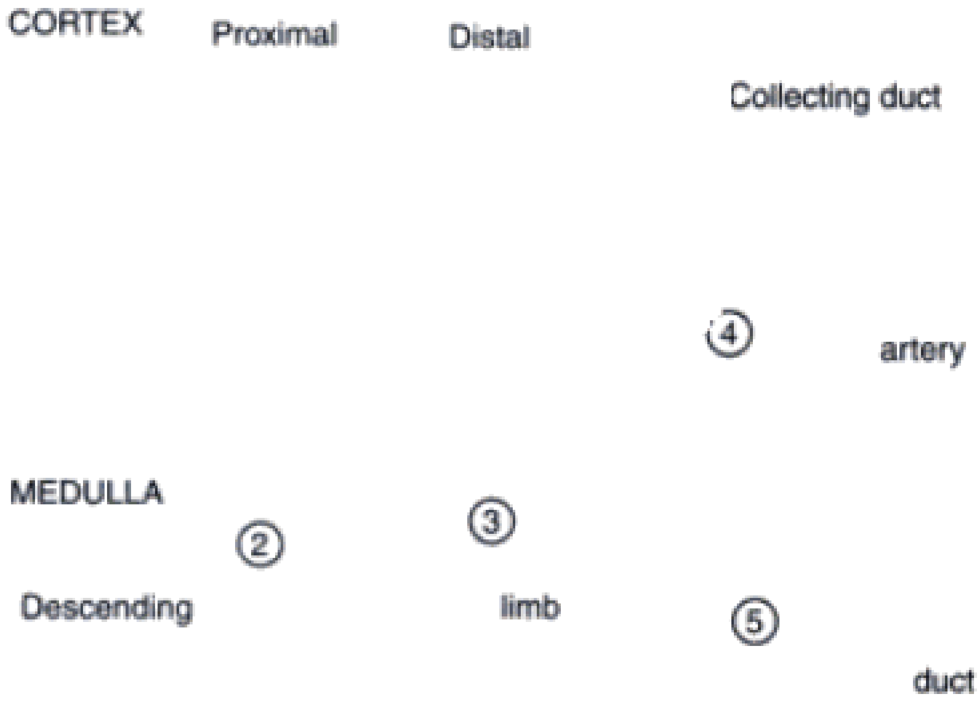


Figure 16–6. Constitutive prostaglandins ensure that intramedullary renal blood flow and urine formation will continue in the presence of decreased renal perfusion. Sites of action are noted by numbers and include shunting of blood from the cortices to the medullary intersitium; stimulation of natriuresis; and inhibition of antidiuretic hormone. The nephrotoxicity of selected drugs reflects inhibition of renal prostaglandins.

dramatic. Excretion is more rapid in alkaline urine, which might be used therapeutically to treat acute aspirin intoxication.

Aspirin is characterized by a wide safety margin in most species. The recommended therapeutic range in humans is 100 to 250 μg/mL (Beasley and Buck, 1980). Toxicity occurs if serum salicylate concentrations exceed 300 μg/mL; however, analgesia and antipyresis require concentrations of 20 to 50 μg/mL (Chastain, 1987). Control of inflammation may require concentrations that exceed 50 μg/mL; rheumatoid arthritis in human beings requires concentrations approximating 200 μg/mL. Although the drug concentration necessary to achieve an antithrombotic effect has not been established for aspirin in animals, smaller doses have proved efficacious (e.g., 3 mg/kg). Toxic (acute) overdose is usually manifested as depression, vomiting, hyperthermia, electrolyte imbalances, convulsions, coma, and death, and is more likely in cats due to slow metabolism with accumulation. Acute toxicity includes serious acid-base disturbances due to uncoupling of oxidative phosphorylation. Hyperventilation due to direct stimulation of the respiratory center may be followed by depression at high doses. Bleeding disorders may also be evident (Larson, 1963; Chastain, 1987). Dose-dependent hepatotoxicity may also occur. The effects of NSAIDs on cartilage, which are largely detrimental, have been summarized. Aspirin is among the NSAIDs that have a detrimental effect on cartilage metabolism.

Oral salicylates such as sulfasalazine have been used to treat chronic inflammatory conditions of the bowel. Although their mechanism of action is unclear, splitting of the diazo bond by colonic bacteria to yield sulfapyridine and 5-aminosalicylic acid (5-ASA) may be involved. The 5-ASA is considered to be the active moiety (Robinson, 1989b). Both the sulfapyridine and sulfasalazine (up to 25%) are absorbed from the small intestine, but most of the 5-ASA remains in the colon. That absorbed (approximately 20% in humans) is rapidly acetylated and inactivated by either the colonic mucosa or liver. Newer products composed principally of 5-ASA are being investigated for the treatment of chronic inflammatory bowel diseases (Robinson, 1989b). Alternative methods of delivery of these compounds such that side effects are minimized are also being studied (Takaya et al., 1997).

Dogs

In dogs, aspirin is distributed to a volume ranging from 0.4 to 0.6 L/kg. Bioavailability probably varies with the manufacturer as well as the preparation and ranges from 68% to 76% (Morton and Knottenbelt, 1989). The bioavailabilities of plain, buffered, and enteric-coated aspirin (25 mg/kg) do not appear to vary markedly, although plasma salicylate concentrations were most variable for the enteric-coated preparation (Lipowitz et al., 1986). After several doses of 25 mg/kg at 12-hour intervals, the biologic half-life of aspirin is 7.5 hours in dogs. This time increased to a mean of 12.2 hours, however, when the dosing interval was decreased to 8 hours (Konturek, 1986). In another study, the elimination half-life of aspirin varied after IV injection of 36 to 60 mg/kg, ranging from 2.2 to 8.7 hours.

The dose necessary to maintain clinical control of various lamenesses in dogs in one study ranged from 23 to 86 mg/kg twice daily, resulting in plasma drug concentrations ranging from 71 to 281 μg/mL (Jezyk, 1983). Marked individual variability in drug elimination among animals suggests that therapeutic drug monitoring may be useful to ensure that therapeutic drug concentrations have been achieved and that toxic concentrations (> 300 μg/mL) are avoided (Morton and Knottenbelt, 1989). One study in clinical patients found that plasma salicylate concentrations correlated with response (Morton and Knottenbelt, 1989). When 25 mg/kg is administered at 8-hour intervals, therapeutic concentrations can be expected to be maintained throughout the dosing interval. Gastrointestinal side effects of aspirin in dogs appear to be dose and preparation related (Shaw et al., 1997; Lipowitz et al., 1986), and may be decreased by using special preparations. Doses of 25 mg/kg of plain aspirin caused mucosal erosions in 50% of dogs that received plain aspirin, whereas there was minimal damage in animals receiving buffered and coated preparations (Lipowitz et al., 1986).

Cats

As a phenol, aspirin is a compound that undergoes glucuronidation poorly in cats (Larson, 1963; Yeary and Swanson, 1973). The plasma elimination half-life of aspirin in cats is 37.6 hours (Davis et al., 1973). The elimination of aspirin may be dose dependent: The half-life is 22 to 27 hours after doses of 5 to 12 mg/kg but 45 hours after administration of 25 mg/kg (Hochberg, 1989). No clinical signs of toxicosis occurred in one study in which cats were treated with 25 mg/kg every 48 hours (Yeary and Swanson, 1973).

Carprofen

Dogs

Carprofen is a proprionic acid-derived NSAID approved in the United States for use in dogs for the treatment of osteoarthritis (Fox and Johnston, 1997). The drug is approved for use in dogs and cats in selected countries outside of the United States. Like other NSAIDs, carprofen has antipyretic, analgesic, and anti-inflammatory effects (Fox and Johnston, 1997). Its potency is equal to that of indomethacin and surpasses that of aspirin or phenylbutazone (Fox and Johnston, 1997), and doses subsequently are smaller for carprofen than for these NSAIDs. Carprofen appears to be equally or more effective than most other NSAIDs studied for the control of inflammation, and it has proved effective for control of the pain associated with the inflammation of osteoarthritis (Vasseur, 1995).

The mechanism of action of carprofen is not certain, but, unlike other members of its class (e.g., ibuprofen, ketoprofen, and naproxen), it may be relatively selective for inhibition of COX2. With canine platelet-derived COX1 and macrophage-like cell COX2, the ratio of COX1 to COX2 IC_{50} (concentration that caused 50% inhibition) for the racemic mixture (that available in the commercial preparation) was 129; the ratio was 181 for the S isomer and more than 4.19 for the R isomer (Ricketts et al., 1998). These differences in COX inhibition may explain the apparent safety of carprofen compared with other NSAIDs in dogs and with safety in the dog compared to that in humans, for whom the ratio is less than 1.

Like other NSAIDs, carprofen is highly protein bound. Carprofen is metabolized by the liver and in dogs is characterized by a half-life of 10 hours. Although this is shorter than the 14-hour elimination half-life of etodolac, which is approved for once-daily use, carprofen may also be effective when administered once daily. The dispositions of the two enantiomers have been studied (Priymenko et al., 1998) in dogs. Both the R isomer (72%) and the S isomer (92%) are extensively excreted in the bile, but enterohepatic circulation appears to be relatively specific for the S isomer (the isomer characterized by a very favorable COX2 specificity), probably due to greater glucuronidase-resistant isoglucuronides for the R isomer (Priymenko, 1998). The mean residence times of the two isomers do not differ, but the clearance and volume of distribution of the S isomer are greater than those of the R isomer (Priymenko et al., 1998).

Even more appealing to efficacy is the safety of carprofen: dogs dosed with more than 10 times the amount necessary to achieve therapeutic concentrations did not develop gastrointestinal side effects when dosed for 2 weeks or when dosed at five times the recommended dose for 52 weeks. In a clinical trial of 70 dogs, 6 of 36 carprofen-treated dogs developed clinical signs indicative of gastrointestinal upset; three dogs that received placebo also developed gastrointestinal signs (Vasseur et al., 1995). Forsyth et al. (1998) compared the gastrointestinal side effects of carprofen (2 mg/kg orally twice daily for 7 days followed by 2 mg/kg once daily), meloxicam (0.2 mg/kg orally once daily), and ketoprofen (1 mg/kg orally every 24 hours) with those in a control group after 28 days of therapy in dogs. The fewest and least severe gastroduodenal lesions evidenced endoscopically were in the carprofen and control group, but there was no statistical significance between the three NSAIDs and the control group, making interpretation difficult. No animals revealed clinical signs associated with gastrointestinal upset. Reimer (1999) found etodolac and carprofen to be equal to placebo and all three to cause fewer gastric lesions than aspirin when dosed at labeled doses for 28 days. Factors contributing to differences among dogs and species in susceptibility to carprofen-induced gastrointestinal ulceration are not known. Yet to be studied are differences in toxicity among COX2 enantiomers. The incidence of gastrointestinal toxicity is more likely to occur at higher doses. Certainly, older animals should be considered predisposed to gastrointestinal side effects. In all animals, clients should be counseled regarding the potential gastrointestinal side effects of this drug and instructed to discontinue it at the first sign of anorexia, nausea, or diarrhea. The veterinarian should then be contacted.

Hepatotoxicity reflecting acute hepatic necrosis has been reported as an unexpected adverse effect of carprofen in dogs (MacPhail et al., 1998). Approximately 1 year after its approval, reports of gastrointestinal toxicity led Pfizer to address concerns regarding side effects in a Technical Report (1998). Of the 1 million dogs receiving carprofen, an incidence of 0.2% suspected side effects was reported, with 0.02% involving the liver. Although 33% of animals affected in initial studies were Labrador retrievers, this number was not corrected for the prevalance of this species.

Hepatopathy has been diagnosed in all breeds of dogs receiving carprofen. At least 70% of afflicted animals were considered geriatric, suggesting that geriatric animals are predisposed, perhaps due to decreased hepatoprotective function (e.g., glutathione scavenging of metabolites). Although death has occurred in some animals, timely discontinuation of the drug can lead to complete resolution of biochemical abnormalities. Animals with liver disease in one study also had evidence of renal tubular disease (MacPhail et al., 1998). MacPhail et al. (1998) studied 21 animals and reported clinical signs of anorexia, vomiting, lethargy, diarrhea, polyuria, polydipsia, and hematuria occurring between 5 and 30 days; however, clinical signs did not occur until as long as 60 and 180 days for two dogs. In this study, 13 of the 21 dogs were Labrador retrievers, with dogs ranging in age from 4 to 15 years. The most common clinical laboratory abnormalities included increased activities of serum alanine transaminase, aspartate transaminase, alkaline phosphatase, and bilirubin. Histologic lesions in the liver ranged from mild to severe and consisted of hepatocellular necrosis. Four of the 21 dogs died; those remaining that were hospitalized were treated with supportive therapy, including gastrointestinal protectants. Hepatic disease might be minimized by pretreatment evaluation because lesions appear to occur within the first several weeks of therapy. Because lesions appear to occur within the first several weeks of therapy, monitoring (clinical laboratory tests) for hepatic damage and hepatic function (bile acids) at weekly or biweekly intervals for the first month is recommended, particularly in predisposed (e.g., geriatric) animals. Monitoring should continue at intervals of 2 to 4 weeks for 3 months. Animals receiving phenobarbital have been reported to be more susceptible to hepatotoxicity. Although this has yet to be validated scientifically, induction of hepatic drug metabolizing enzymes by phenobarbital is likely to increase the risk of toxicity. Use of hepatoprotective agents such as *N*-acetylcysteine (a glutathione precursor) or S-adenosylmethionine may be beneficial during initial hepatic damage.

The effect of carprofen on cartilage physiology is questionable and appears to be biphasic (Benton et al., 1997). In vitro studies with canine chondrocyte cell cultures revealed that carprofen increases the rate of polysulfated glycosaminoglycans (PGAG) synthesis at synovial fluid concentrations (≤ 10 μg/mL) achieved in human patients receiving a therapeutic dose of carprofen. Inhibition of PGAG synthesis, however, occurs at concentrations of 20 μg/mL or more (Benton et al., 1997). Concentrations that occur in dog synovial fluid after administration of a therapeutic dose of carprofen have not been determined. Thus, the most likely effect of carprofen on cartilage is not apparent.

Cats and people do not appear to enjoy the same level of safety of carprofen as do dogs. The drug should be used short term only in cats.

Carprofen is approved for use in the treatment of osteoarthritis in dogs (Vasseur et al., 1995). Like other NSAIDs, the risk of gastrointestinal upset should lead to counseling the client regarding the clinical signs associated with gastrointestinal ulceration. Doses should be titrated to the minimum effective. Carprofen is such an effective analgesic that it shows potential for control of postoperative pain (Lascelles et al., 1994, 1998). Studies have shown it to be an effective postoperative analgesic in cats (4 mg/kg subcutaneously) (Balmer et al., 1998) and dogs (Welsh et al., 1997) when administered preoperatively.

Cats

Carprofen is approved for use in cats in select countries outside the United States. The drug's pharmacokinetics have been studied, and the results include a predominance of the R enantiomer, 100% oral bioavailability, and a long elimination half-life (Taylor et al., 1996) following administration of a racemic mixture. Pharmacodynamic evaluation focusing on control of inflammation indicated a dose of 4 mg/kg (Taylor et al., 1996; Lascelles et al., 1995; Balmer et al., 1998). As a postoperative analgesic, carprofen compared favorably with pethidine (meperidine), providing equal but longer analgesia (at least 24 hours) when administered at 4 mg/kg subcutaneously postoperatively (Balmer et al., 1998). However, the relative COX2 selectivity of carprofen that occurs in dogs has not been documented in cats. Duodenal perforation has been reported in cats using oral administration of carprofen following ovariohysterectomy (Runk et al., 1999).

Etodolac

Etodolac is a pyranocarboxylic acid that has shown potent NSAID activity by inhibiting chondrocyte and synoviocyte biosynthesis of PGE_2. In in vitro studies, its COX1:COX2 ratio varies. The ratio using human cells appears to favor safety (Glaser, 1995), although studies using canine cells (Ricketts et al., 1998) reveal the opposite. Ricketts et al. (1998) reported a COX1:COX2 ratio of only 0.517 compared with 129 for carprofen; however, clinically etodolac appears safer than the ratio suggests. In dogs, the drug appears to undergo enterohepatic circulation, resulting in an elimination half-life of 14 hours (Cayen et al., 1981), which is sufficiently long to allow once-daily dosing. When dosed at 10 to 15 mg/kg once daily, it appears to be effective yet safe for controlling lameness associated with hip dysplasia (Budsberg et al., 1966). Its effect on cartilage metabolism has not been well documented. Because of its longer half-life and enterohepatic elimination, etodolac may be associated with a greater risk of gastroduodenal ulceration than other drugs that also appear to be selective COX2 inhibitors, although clinically there appears to be no support for increased risk compared with carprofen.

According to the package insert, six of eight dogs developed gastrointestinal erosions and subsequently died after etodolac administered at five times the recommended dose for 6 to 9 months. Gastrointestinal ulceration can be expected in animals receiving 2.5 to 3 times the recommended maximum dose. Five of six dogs developed excessive bleeding when receiving etodolac at the recommended dose, although the duration of therapy was not clear from the package insert. Liver disease such as that associated with carprofen has not been reported with etodolac, although I am aware of two cases of acute hepatopathy that were associated with etodolac therapy. In one patient, lesions resolved with discontinuation of the drug; the second died from the illness. As with carprofen, histologic signs were nonspecific. Use of etodolac has not yet, however, equalled that of carprofen, and conclusions cannot be made regarding the relative safety of the two products at this time.

Meloxicam

Meloxicam, like prioxicam, is a member of the oxicam group of NSAIDs approved for use in tablet and oral suspension forms in Canada and Europe in dogs and cats. The COX2:COX1 ratio for meloxicam, unlike that for piroxicam, favors selective COX2 inhibition, suggesting that it has a wider margin of safety than most other NSAIDs (Engelhardt et al., 1996a–c; Hare et al., 1998), a suggestion supported by clinical studies. The drug is more potent (although not necessarily more efficacious) than aspirin, indomethacin, and piroxicam; hence, its dose is smaller. Its efficacy in treatment of locomotor disorders in dogs compares favorably with other NSAIDs (Van Bree et al., 1994; Hare et al., 1998). Like other NSAIDs, meloxicam is highly (97%) protein bound and undergoes hepatic metabolism. Its elimination half-life is relatively long in dogs at 20 to 30 hours, allowing once-daily administration. Hence, a loading dose of 0.2 mg/kg is given the first day, followed by a maintenance dose of 0.1 mg/kg. The cautious clinician may want to avoid the loading dose in the event that the pet owner neglects to reduce it to the maintenance dose; as with most drugs, the selectivity enjoyed with the mechanism of action of this or any selective NSAID is likely to be lost at high doses. Safety of the drug has been established at four times but not six times the recommended dose when administered for 4 weeks. It currently is not available in the United States.

Phenylbutazone

Phenylbutazone is a weakly acidic, lipophilic NSAID approved for use in dogs. Inhibition of the AA cascade by phenylbutazone occurs after conversion to reactive intermediates at the level of PGH synthase and prostacyclin synthase. Prostanoid-dependent swelling, edema, erythema, and associated pain are reduced by phenylbutazone (Tobin et al., 1986). Phenylbutazone has been associated with some attenuation of some clinical signs associated with endotoxic shock in experimental models (Moore et al., 1986; Jarlov et al., 1992).

Bioavailability after intramuscular administration of phenylbutazone is less than that after oral administration in most species studied because of precipitation in the neutral pH of muscle (Williams, 1988; De Backer et al., 1980; Tobin et al., 1986). Phenylbutazone is metabolized by the liver, with less than 2% of the drug being excreted as a parent compound in the urine in some species. Its major metabolites are oxyphenylbutazone, which is less active than phenylbutazone, and inactive γ-hydroxyphenylbutazone (Tobin et al., 1986; Mills et al., 1995a, b). Reported adverse reactions caused by phenylbutazone include bleeding dyscrasias, hepatopathy, and nephropathy (primarily in horses) (Tobin et al., 1986; Carlisle et al., 1968; Murray, 1985; Tandy and Thorpe, 1967). Phenylbutazone has chondrodestructive effects (Kalbhen, 1988; Jolly et al., 1995).

Dogs

Despite approval of the oral preparation for use in dogs, there is little information regarding the use of phenylbutazone in dogs. The half-life in plasma (7.3 to 18 hours) is shorter than that in tissues (20 hours), although peak concentrations in tissues (13 to 20 μg/mL) were approximately one third of those in plasma (49 to 75 μg/mL) (Zech et al., 1993) following a dose of 15 mg/kg orally. The elimination half-life (in greyhounds) is 6 to 7 hours (Mills et al., 1995a, b). Dogs apparently are more tolerant of phenylbutazone than humans. When used to treat racing greyhounds, caution may be necessary regarding drug testing. One study (Thomas et al., 1997) has documented that phenylbutazone can be detected in the urine of greyhounds after topical administration in a commercially available cream.

Toxicity manifested as hemorrhage, biliary stasis, and renal failure has been reported in one dog receiving close to recommended doses (Tandy and Thorpe, 1967; Watson et al., 1980; Weiss and Klausner, 1990). For reasons not explained, the package insert notes a total maximum dose and requires the drug to be discontinued slowly. Bone marrow dyscrasias (including neutropenia) also have been reported.

Cats

Although phenylbutazone has been used in cats, a high incidence of toxicity suggests extreme caution. One hundred percent of cats treated with 44 mg/kg daily became anorectic at 2 to 3 days, with 80% mortality at 2 to 3 weeks. Toxicity occurs primarily in the bone marrow and is characterized by decreased erythroblastic activity and possible interference with myeloid maturation. Gastrointestinal damage, nephrotoxicity, and hepatotoxicity also occur (Carlisle et al., 1968).

Flunixin Meglumine

Flunixin meglumine is a nicotinic acid derivative approved for use in the horse. Described as a potent analgesic agent, it has been used to control pain that might otherwise respond only to opioids. It is particularly useful for visceral pain. In addition to its analgesic effects, flunixin meglumine has been studied and cited for its antiendotoxic effects in experimental models of septic shock in several species (Hardie et al., 1983; Moore et al., 1986; Templeton et al., 1987; Jarlov et al., 1992; Davidson et al., 1992).

After an intravenous dose of 1.1 mg/kg in healthy dogs, flunixin is characterized by an elimination half-life of 3.67 ± 1.2 hours and a clearance of 0.064 ± 0.01 L/h/kg. Volume of distribution at steady state is 0.18 ± 0.08 L/kg (Hardie et al., 1985). Although the mode of action has not been documented, flunixin is specifically recommended as an analgesic in the treatment of colic in horses and may be useful for control of visceral pain in dogs (e.g., parvovirus) or postoperative pain (Matthews et al., 1996). It also appears useful for the treatment (and especially pretreatment) of endotoxic shock (Lee and Higgins, 1985). It prevents many of the adverse effects caused by administration of endotoxin, thromboxane A_2, and PGI_2 (Hardie et al., 1985). Flunixin meglumine appears to modulate response to septic shock in dogs (Hardie et al., 1983; Davidson et al., 1992; McKellar et al., 1989). In dogs, a dose of 1.1 mg/kg flunixin meglumine blocks PGI_2 production, whereas 2.2 mg/kg improves survival times of septic dogs (Hardie et al., 1985). Pharmacokinetics of flunixin in septic dogs does not appear to differ from that of control dogs (Hardie et al., 1985). Toxicity, most commonly manifested as gastrointestinal upset, limits use of this drug in dogs to 2 to 3 days. Doses at three to five times those recommended caused gastrointestinal disturbances in one study.

Ketoprofen

Ketoprofen is a propionic acid NSAID approved for use in humans and horses. Because ketoprofen is a strong inhibitor of cyclooxygenase, it has been ascribed powerful anti-inflammatory, analgesic, and antipyretic properties. In human patients suffering from rheumatoid arthritis, ketoprofen has been shown as efficacious as aspirin, naproxen, aspirin, indomethacin, ibuprofen, diclofenac, and piroxicam (Avouac and Teule, 1988). Similar results occurred in cancer patients receiving either aspirin/codeine combinations or ketoprofen (Stambough and Drew, 1988). For control of postoperative pain, ketoprofen has proved equally effective as pentazocine and meperidine (Avouac and Teule, 1988) and equally effective but longer in duration than acetaminophen/codeine combinations (Turek and Baird, 1988). Although not firmly established, the efficacy of ketoprofen has been attributed to its ability to inhibit some lipoxygenases and thus formation of leukotrienes (Williams and Upton, 1988). Ketoprofen is also a powerful inhibitor of bradykinin (Williams and Upton, 1988).

Ketoprofen is rapidly absorbed from the gastrointestinal tract. Although peak plasma drug concentrations are lower in dogs after oral than IV administration, mean residence times (4.59 vs. 3.81 hours, respectively) were not different (Schmitt and Guentert, 1990). Although peak drug concentrations may be less, bioavailability does not seem to be impaired by food. As with other NSAIDs, ketoprofen is approximately 99% protein bound, principally to albumin. Elimination reflects metabolism to inactive metabolites by the liver and excretion as the glucuronide conjugate in the urine (Williams and Upton, 1988). Drug interactions involving ketoprofen have not yet been documented (Cailleteau, 1988).

Adverse reactions to ketoprofen in humans occur in approximately 30% of the patients studied (Beaver, 1988; Stambough and Drew, 1988). The most frequent complaint was upper gastrointestinal upset. Other commonly encountered side effects include CNS reactions, such as headaches and dizziness, and nephritis. Side effects were severe enough in one report that therapy was discontinued in approximately 13% of patients (Cailleteau, 1988). Alternative preparations, such as rectal suppositories, have been formulated for ketoprofen in order to reduce the incidence of gastrointestinal toxicity (Schmitt and Guentert, 1990). Ketoprofen is not approved for use in small animals in the United States but is approved for both dogs and cats in Canada and Europe. We have seen gastrointestinal upset in some dogs treated with ketoprofen that was assumed to be drug induced suggesting that, like all NSAIDs, care be taken when using the drug.

The use of ketoprofen as an analgesic and antipyretic has been studied in cats. The antipyretic effect of ketoprofen (2 mg/kg subcutaneously followed by 1 mg/kg once daily orally) in febrile cats was rapid, being evident in 4 hours with temperatures normalized at that time (Glew et al., 1996). Temperatures did not change in the antibiotic-only treated cats. The use of ketoprofen as an analgesic is variable (Slingsby and Waterman-Pearson, 1998). In cats subjected to ovariohysterectomy, ketoprofen (2 mg/kg subcutaneously) compared favorably with buprenorphine (0.006 mg/kg or 6 μg/kg intramuscularly) and mepiridine as gas anesthesia was discontinued. Response was based on visual analogue scores and overall clinical assessment. Response was equal to that of buprenorphine at 4 hours and better at 8 hours. Response was better for both drugs compared with the control at both 4 and 8 hours but still present for buprenorphine only compared with control at 18 hours.

Piroxicam

Piroxicam is an oxicam NSAID approved for humans that has been used to treat osteoarthritis in dogs. More recently, it has received attention for its ability to reduce the size of tumors (transitional cell tumors and others) in dogs (Braun et al., 1987; Knapp et al., 1992, 1994, 1995). This latter effect may result from both immunomodulation and inflammation at the tumor site. Piroxicam may interact by an additive or synergistic action with anticancer drugs to cause tumor cell death. Piroxicam is a potent anti-inflammatory in musculoskeletal conditions. Oral absorption is rapid, with 100% bioavailability (Galbraith and McKellar, 1991). Distributed to a volume of 0.34 kg, its half-life of 40 to 45 hours in dogs is similar to that in humans (Galbraith and McKellar, 1991). Although the LD_{50} of piroxicam is greater than 700 mg/kg in dogs, gastric lesions and renal papillary necrosis have occurred in dogs receiving 0.3 to 1 mg/kg daily (Galbraith and McKellar, 1991; Knapp et al., 1992). The ratio of COX2:COX1 suggests that gastrointestinal toxicity occurs. Little evidence of toxicity (gastrointestinal or bleeding), however, was noted after administration of 0.3 mg/kg every other day (Galbraith and McKellar, 1991; Knapp et al., 1992). Extrapolation of human use to dogs should be done cautiously because of possible differences in volume of distribution, therapeutic concentrations, or safety margin.

Ketorolac

Ketorolac is an NSAID approved for use in human patients. In contrast to many NSAIDs, ketorolac is only moderately effective as an anti-inflammatory (Insel, 1996). It is a potent analgesic, however, that has been described as equivalent to morphine. As such, it has been used as a perioperative analgesic in dogs (Paddleford, 1999). In people, ketorolac causes gastrointestinal upset, and similar side effects occur in dogs. Ketorolac appears better than butorphanol and equal to flunixin meglumine for control of postoperative pain. Despite its potential efficacy as a postoperative analgesic, however, 1 of 21 dogs developed gastrointestinal ulceration after a single dose (Matthews et al., 1996). Therefore, recommendations are to limit use to one to two treatments, or 3 days. The kinetics apparently have not been reported in dogs. Other side effects reported in people include dizziness, headache, nausea, and pain at the site of injection (Insel, 1996). Caution should be taken particularly in the perioperative patient, which is more likely to be dependent on renal prostaglandins during the surgical procedure.

Naproxen

In dogs, naproxen is rapidly absorbed after oral administration, with maximal plasma drug concentrations occurring at 0.5 to 3 hours. Bioavailability ranges from 68 to 100%. Naproxen is 99% bound to serum proteins in dogs resulting in a volume of distribution of 0.13 L/kg. Total body clearance is 0.021 mg/kg per minute. Notably, compared with 12 to 15 hours in humans and 5 hours in horses, the elimination half-life of naproxen after IV administration in dogs ranges from 45 to 92 hours (Frey and Rieh, 1981). Peak concentrations in dogs following oral administration of 5 mg/kg were 40 to 50 μg/ml. Tissue concentrations paralleled plasma concentrations with a peak of 20 to 30 μg/ml; concentrations declined over a period of 200 hours (Zech et al., 1993). Extensive enterohepatic circulation has been credited as the cause for prolonged elimination in dogs. Because of its long half-life, naproxen need only be given once daily to every other day. Although a loading dose has been recommended, the gastrointestinal toxicity of this drug in dogs suggests that a loading dose is not necessary. The dog has been described as the animal most sensitive to naproxen (Frey and Rieh, 1981).

Gastrointestinal toxicity occurs at doses of 5 mg/kg daily (Gfeller and Sandors, 1991). Toxicity appears most likely when plasma drug concentrations exceed 50 μg/mL. If this NSAID is to be used in dogs, doses initially should be low (1–2 mg/kg) and subsequently titrated to the animal's need. Animals should be watched closely for evidence of gastrointestinal upset. Bleeding dyscrasias have also been reported in dogs receiving large doses of naproxen (Frey and Rieh, 1981; Roudebush and Morse, 1981; Gfeller and Sandors, 1991). Naproxen is among the NSAIDs noted to have chondroprotective effects.

Naproxen has been cited for a positive protective effect on articular cartilage. Using a canine experimental model of osteoarthritis, naproxen decreased the loss of proteoglycans and suppressed metalloproteinase activity (Ratliffe et al., 1993).

Ibuprofen

Ibuprofen is a propionic acid derivative that has been used in dogs. Ibuprofen is less effective as an analgesic than is aspirin, perhaps due to differences in binding of cyclooxygenase (reversible for ibuprofen compared with irreversible by aspirin). Ibuprofen is a popular drug in human medicine because it is a very effective anti-inflammatory whose use is associated with a low incidence of gastrointestinal side effects. Gastrointestinal erosions, however, consistently occur in dogs receiving therapeutic doses for 2 to 6 weeks.

Ibuprofen is rapidly absorbed in dogs after oral administration, with peak plasma drug concentrations occurring between 0.5 and 3 hours and bioavailability ranging from 60 to 80% (mean 77%). Volume of distribution is 0.164 L/kg. Plasma elimination half-life after oral or IV administration is 4.6 + 0.8 hours and clearance is 0.49 mL/min/kg. Pharmacokinetics are similar at doses of 5 and 10 mg/kg (Scherkl and Frey, 1987). A dose of 12 to 15 mg/kg is, however, necessary to achieve therapeutic concentrations as reported in humans (Scherkl and Frey, 1987). After repetitive administration of this dose, plasma drug concentrations decrease despite no change in drug half-life (Scherkl and Frey, 1987).

Vomiting occurs commonly after several (2 to 6) days of ibuprofen therapy in dogs with either the gelatin or enteric-coated capsules (Scherkl and Frey, 1987). Gastrointestinal inflammation and gastric erosions have been documented after administration of 8 mg/kg daily despite the lack of clinical signs of toxicity (Scherkl and Frey, 1987). Because gastric lesions occur at doses less than those necessary to achieve therapeutic concentrations, ibuprofen is not recommended for use in dogs.

Meclofenamic Acid

Meclofenamate is an anthranilic NSAID available as a palatable granular preparation intended to be mixed with food for large animals and as a tablet, and is approved for use in dogs in the United States. Among the NSAIDs, it is noted for its slow onset of action. The effects of meclofenamic acid on cartilage have not been studied. The package insert associated with the label of this drug describes dogs as being exquisitely sensitive to the gastrointestinal ulcerogenic effects of these drugs. Meclofenamic acid appears to have no clear advantage to other drugs for treatment of osteoarthritis in dogs and may be more likely to cause gastrointestinal upset.

Indomethacin

Indomethacin is an NSAID that was developed specifically to abate the inflammatory response to the indolic hormones serotonin and tryptophan (Boynton et al., 1988). As a powerful anti-inflammatory, it became a standard for comparison with other drugs. In humans, toxicities are not serious, but CNS side effects are undesirable (Boynton et al., 1988). The incidence of gastrointestinal hemorrhage after administration of indomethacin at doses of 2 to 5 mg/kg precludes its clinical utility in dogs. In one study, all dogs developed melena within 1 week of receiving 2 mg/kg daily; 60% of these animals had gastric ulcers (Ewing, 1972).

Acetaminophen

Acetaminophen (paracetamol) is a coal tar analgesic used in human medicine as an effective alternative to aspirin for control of fever and pain. Classically, it is recognized to have poor anti-inflammatory activity, although this view has become more controversial (Mburu et al., 1988). Although often classified as an NSAID, its mechanism does not involve inhibition of cyclooxygenase. Rather, acetaminophen interferes with the endoperoxide intermediates (PGG_2, PGH_2) of AA conversion. Its relatively weak anti-inflammatory activity has been attributed to the high concentrations of peroxides that occur in peripheral inflammatory lesions. Acetaminophen may be more effective against inflammatory conditions in the CNS.

The major disadvantage to the use of acetaminophen in veterinary patients is the narrow safety margin that characterizes its use in cats. The drug is normally conjugated with glucuronide and to a lesser degree with sulfate. Drug that is not conjugated is metabolized by phase I microsomal enzymes to cytotoxic oxidative metabolites. Intracellular glutathione normally scavenges the metabolites, but in the case of overdose or glucuronide deficiency (as with the cat), the formation of toxic metabolites overwhelms the glutathione scavenging system. In cats, methemoglobinemia is the most common indication of toxicity, although centrolobular hepatic necrosis may also occur. Treatment of acetaminophen toxicity includes administration of antioxidants, including *N*-acetylcysteine, a precursor of glutathione, and ascorbic acid (vitamin C) (St. Omer and McKnight, 1980; Cullison, 1984; Savides et al., 1985). The administration of cimetidine, a microsomal enzyme inhibitor, will reduce the formation of toxic metabolites and will result in clinical improvement if given within 48 hours of acetaminophen administration (Jackson, 1982; Ruffalo and Thompson, 1982).

Acetaminophen (15 mg/kg every 8 hours) may be as effective as aspirin for the control of postoperative pain and inflammation in dogs. An extended relief formulation has proved useful (20 to 30 mg/kg every 8 to 12 hours) at a longer interval (Johnston and Budsberg, 1997). Acetaminophen also can be combined with opioids, particularly codeine (dose based on codeine at 1 to 2 mg/kg orally every 8 to 12 hours). Acetaminophen appears to be safe in dogs. At daily doses of 0.5 g every 8 hours (average weight 18 kg), acetaminophen causes no clinical signs of adverse drug effects (Mburu et al., 1988). Other studies, however, have shown that adverse reactions (depression, methemoglobinemia, and vomiting) can occur at higher (100 mg/kg) doses (Hjelle and Grauer, 1986; Savides and Oehme, 1983). In another study, 900 mg/kg IV caused fulminant hepatic failure in dogs (Francavilla et al., 1989).

Treatment of Osteoarthritis

Osteoarthritis Defined

Degenerative joint disease (DJD), or osteoarthritis (OA), is defined as a loss of articular cartilage and chondrocyte death. It is a noninflammatory disorder primarily because inflammation does not play a significant role in the onset of the disease process. Although the role of inflammation in the pathogenesis of the disease is also limited compared with other joint disorders (i.e., sepsis or immune-mediated diseases), the role of inflammation is sufficient such that drugs that modify inflammation have become important in the management of DJD. However, the concept of chondroprotection in the damaged joint has become a focus for therapy, as have agents that modify the disease process.

Degenerative joint disease is a progressive disease, characterized by degeneration and destruction of articular cartilage (Gardner, 1983; Jones and Doherty, 1992). Certain conditions are predisposed to cause secondary DJD, although it can occur as the primary disorder. Secondary DJD can develop as a result of abnormal joint mechanics (e.g., instability) or direct trauma.

Cartilage Physiology and Pathophysiology

Normal cartilage is avascular and tightly adheres to cortical bone (Vaughan-Scott and Taylor, 1997). A load-bearing and gliding surface of the joint is formed such that a frictionless surface occurs throughout the range of motion of the joint. The fibrous capsule of the joint contains a layer of synovial cells that are very vascular and serve as a selective membrane precluding passage of molecules greater than 12,000 molecular weight. Synovial fluid produced by the cells lubricates and nourishes cartilage. Hyaline cartilage contains a small number of chondrocytes that synthesize the matrix in which they are embedded. The matrix is composed of collagen fibers interspersed in a well-structured manner with proteoglycan aggregates of varying molecular weights (Fig. 16–7). Proteoglycans are comprised of glycosaminoglycans encircling a core protein. The proteoglycan complex in turn is bound (by a link protein) to hyaluronic acid. Chondroitin sulfate is the principal proteoglycan of mature cartilage, with other sulfates (e.g., keratin, dermatan) making up the remainder. Chondroitin sulfates are glycosaminoglycans composed of alternating sulfated residues of a glucuronic acid and a galactosamine. Sources of chondroitin sulfate for commercial purposes include bovine trachea, nasal septum, and shark cartilage. Proteoglycans are large molecules that trap water, thus maintaining the gel-like consistency of cartilage, and act as an elastic shock absorber. Chondrocytes are very metabolically active, constantly breaking down and resynthesizing proteoglycan and collagen. The substrates and energy for these activities are transported to, and waste material from, the cartilage by a synovial "pump" mechanism.

The initial insult leading to cartilage degeneration may vary (i.e., injury, congenital malformation, chronic overload, age), but the sequence of events is similar. The changes occur well before clinical (including radiographic) signs are evident. The initial lesion in osteoarthritis occurs in cartilage. Chondromalacia (softening of the cartilage) occurs early in the course of disease. Collagen turnover is markedly increased by the chondrocytes; reparation may not yield the appropriate (type II) collagen. Ultimately, collagen loss may predominate. Species differences in the repair of collagen are likely to exist. Proteoglycans are also lost as DJD progresses. Initially, proteoglycan synthesis is markedly increased, but the normal ratios of high-molecular-weight versus low-molecular-weight proteoglycan may not be maintained. Eventually, proteoglycan synthesis markedly decreases. Hyaluronic acid concentrations also decrease.

The loss of cartilage matrix is mediated, in part, by proteolytic enzymes such as metalloproteases, including collagenases, stromelysin, and aggrecanase, and lysosomal enzymes released (stimulated by IL-1 or TNF) by synovial cells or chondrocytes. Interleukins 1 and 6, TNF, and nitric oxide also act as cellular or molecular mediators (Pelletier et al., 1993, 1995; Mitchell et al., 1997; Singer et al., 1995). Mediators (eicosanoids, IL-1, and TNF) act to upregulate catabolic enzymes of destruction while downregulating mediators that inhibit catabolic actions (Pelletier et al., 1995). The catabolic process of cartilage degradation worsens as these enzymes are released. Chondrocyte death may occur early in the process of DJD. Synovial cells phagocytize the products of degradation and initiate a (chemical) inflammatory process. Collagen is exposed; fissures develop in the cartilage. Local tissue degradation increases, and leukocytes are activated, eventually leading to a viscous cycle of degradation and inflammation.

As cartilage continues to bear weight, mechanical destruction and physiologic changes continue. The damaged cartilage cannot bear weight appropriately, and subchondral bone is exposed to forces that normally would be dampened. Subchondral sclerosis occurs, and apposing articular surfaces become eburnated. Cartilage homeostasis is interrupted, limiting access to fluid-containing nutrients. Fluid released into the synovial joint may not be efficiently absorbed. In addition, mediators of inflammation are released by both chondrocytes and synovial cells. The joint becomes painful as a result. Microfractures and fissures allow synovial fluid to penetrate into the bone, with resulting subchondral cyst formation. The damaged cartilage attempts to repair the damage as it occurs by synthesizing new proteoglycan and collagen. Osteoarthritis probably occurs when the catabolic process overwhelms the repair process.

Drug Therapy

The goals of drug therapy for DJD should be (1) to control pain, (2) to increase mobility, (3) to prevent continued degradation of the joint, and (4) to provide support to reparative processes. In addition to drug therapy, dietary management (i.e., weight control) and exercise control should be implemented, and surgical options should be considered when appropriate. Mechanisms of therapeutic drugs designed to retard the deterioration of DJD include inhibition of synovial cell–derived cytokines and chondrocyte-derived degradative enzymes, inactivation of superoxide radicals, stimulation of matrix synthesis, and enhancement of synovial fluid lubrication (Pinals, 1992; Altman et al., 1989).

Advances in the pathophysiology of DJD (osteoarthritis) have provided new therapeutic foci. The progressive degeneration of articular cartilage that characterizes this disease reflects an imbalance between cartilage matrix synthesis and breakdown. The role of inflammation in the pathophysiology of DJD is controversial. The impact of NSAID therapy can be a two-edged sword: the effects may be either harmful or beneficial, depending on the drug. The primary effect of NSAIDs in the disease is probably analgesic rather than anti-inflammatory (Pinals, 1992). A number of other anti-inflammatory drugs have been studied for their efficacy in the treatment of DJD, and their use for treatment of osteoarthritis has been summarized. The dose of NSAID needed to control pain associated with osteoarthritis may vary greatly among animals. Drugs can control pain not associated with inflammation at doses lower than those necessary to control pain associated with inflammation. On the other hand, for some animals, evidence of pain may be controlled only if inflammation is successfully controlled. The choice of the most appropriate NSAID should be based on both efficacy and safety.

Until relatively recently, little justification existed for the selection of one NSAID over another for treatment of osteoarthritis in dogs. Approval of carprofen or etodolac (meloxicam in Canada) has, however, provided a realistic first-choice drug. If carprofen is not used, the basis for selection is tenuous. Aspirin probably remains the second drug of choice simply because it is a "known"; in countries in which ketoprofen is approved, it may be the second choice. For long-term use, chondroprotection should also be considered. Caution is recommended with use of those drugs particularly likely to cause gastrointestinal upset (naproxen, piroxicam), and doses should always begin low and be titrated upward to a clinically effective yet safe dose. The higher the dose and the older the animal, the more important cytoprotective drugs should be considered on a preventative basis. These include sucralfate or misoprostol. Antisecretory drugs might also be considered and might be more cost effective. These drugs, however, only control gastric acid secretion and do not support the cytoprotective needs of the gastrointestinal mucosa. For acute conditions (or "flare-ups"), a reasonable approach might be the use of an NSAID for control of pain (and inflammation) with the intent of discontinuing it as rapidly as possible. Disease-modifying agents might be considered simultaneously in order to decrease the amount of time that an NSAID is necessary. Regardless of the recommended dosing regimen, the regimen of any NSAID should be titrated down (or the interval prolonged) to establish the minimum effective dose necessary to control the animal's pain. Although doses can be increased, extreme caution is recommended when surpassing the recommended dose of even the "selective" COX2-inhibiting NSAID.

Selection of an NSAID for treatment of osteoarthritis in cats is more difficult. Aspirin remains the drug of choice until comparative studies regarding the safety and efficacy of other NSAIDs for cats (e.g., ketoprofen, carprofen, and flunixin meglumine) justify their preferred use in cats. Disease-modifying agents also should be used in cats.

NSAIDs should never be used in combination. Drug interactions (including competition for protein-binding sites) are likely to lead to an increased risk of gastrointestinal toxicity. In addition, despite some studies that might suggest otherwise (Kietzmann et al., 1996), NSAIDs probably should not be combined with glucocorticoids. The use of glucocorticoids for the treatment of osteoarthritis is discussed in Chapter 17. In general, these drugs should not be used because of their chondrodestructive effects, which are likely to occur at clinically used doses.

DISEASE-MODIFYING AGENTS: CHONDROPROTECTANTS

A number of compounds are able to modify the progression of osteoarthritis, most commonly due to support of the cartilage. These products help achieve the goals of preventing further degradation and providing support for the reparative cartilage. Evidence exists that clearly supports the use of these products as sole or adjuvant therapy in the treatment of the damaged joint (see discussion of recommendations regarding the use of disease-modifying agents in the treatment of joint disease).

Injectable Products

Polysulfated Glycosaminoglycans

Efforts to treat osteoarthritis have focused on drugs that favorably shift the balance between degradation and synthesis of cartilage matrix. Two compounds composed of polysulfated glycosaminoglycans (PGAGs) are available in the United States and Canada: adequan and pentosan polysulfate. Hyaluronic acid (Legend) is also a PGAG but differs in structure sufficiently to be addressed separately. Because of similarities in structure, however, the dispositions of these drugs are similar, and their mechanisms of action often overlap. On the other hand, their role in the physiology and function of the joint are sufficiently different that combination therapy in the damaged joint might be considered. The use of these compounds often is considered only for osteoarthritis, but in fact they should be considered for use regardless of the cause of joint damage—trauma, immune-mediated diseases, septic or drug-induced damage, surgery (including prophylaxis)—and prophylactically in the animal predisposed to joint damage because of conformation or intensive training. Because PGAGs are responsible for normal functions in a variety of body tissues, their potential applications include disorders other than osteoarthritis (e.g., interstitial cystitis and glomerulonephritis).

Chemistry

Polysulfated glycosaminoglycan (adequan) is a polymeric chain of repeating units of hexosamine and hexuronic acid. Considered a hypersulfated compound, approximately 14% of the drug is sulfated. It is extracted and purified from bovine tracheal tissues (White, 1988). Normal cartilage matrix is composed of proteoglycan complexes, collagen, and water. Side chains of glycosaminoglycans (keratin and chondroitin) are attached to the core protein of the proteoglycan molecule by a strand of hyaluronate (Fig. 16–7). Water trapped in between these complexes accounts for the resiliency of cartilage. Polysulfated glycosaminoglycans closely mimic the proteoglycan complexes found in normal articular cartilage.

Pharmacologic Effects

Polysulfated glycosaminoglycans appear to be chondroprotective in both in vitro and in vivo models. In vivo models have included chemically and traumatically induced cartilage damage (Francis et al., 1989; Hannan et al., 1987). Cartilage degradation is retarded in the presence of PGAG. Although the mechanisms of these protective actions are not known, chondrocyte proliferation and matrix biosynthesis appear to be important (Hannan et al., 1987). Collagen, proteoglycan, and hyaluronic acid syntheses increase (Nethery et al., 1992). In addition, proteolytic enzymes such as collagenase (Halverson et al., 1987; Nethery et al., 1992), leukocyte elastase (Rao et al., 1990), proteases (White, 1988; Montefiori et al., 1990), and lysozomes are inhibited (Montefiori et al., 1990), although these actions are likely to be complex (Nethery et al., 1992). Complement activity is also inhibited; the degree of inhibition appears to be related to the sulfate load of the chondroitin sulfate matrix (Biffoni and Paroli, 1991). Polysulfated glycoaminoglycans appear to have no effect on the ability of IL-1 to stimulate metalloproteinase activity in cartilage (Arsenis and McDonnell, 1989).

Disposition and Safety

Deposition of PGAG in normal and damaged cartilage has been demonstrated after parenteral administration. Drug that is not retained in cartilage is excreted primarily by the kidneys with minimal degradation of the the parent compound. Toxicity is limited in all species studied. In dogs, the LD_{50} is 1000 mg/kg (White, 1988). Heparin and PGAG are chemically similar. Adverse effects related to the anticoagulant activity of PGAG have been suggested. One study found coagulation times to be prolonged after administration. This suggests that PGAGs should not be administered at the time surrounding a surgical procedure. Heparin-associated thrombocytopenia, a presumed immunologically mediated decrease in circulating platelet numbers, has been reported in human patients receiving PGAG (Greinacher et al., 1992).

Clinical Use

Adequan has been approved for use in dogs for the treatment of osteoarthritis. The drug might, however, be considered in any situation in which the joint has been or will be injured. This includes trauma, elective surgical procedures, and arthritis associated with immune-mediated or infectious conditions. Additionally, PGAGs should be considered in conjunction with NSAIDs for their chondroprotective effects as well as with the intent to potentially discontinue the NSAID. Disease-modifying agents including PGAG or its precursors (see later discussion of nutraceuticals) might also be considered as "preventive" therapy in animals that are likely to develop osteoarthritis for whatever reasons, including conformation problems. Use of these drugs before clinical signs of osteoarthritis develop is likely to offset the time to the need for NSAIDs. In patients with osteoarthritis, the time to clinical response is likely to be directly related to the severity of disease. Treatment that is begun before the joint is markedly damaged is more likely to be successful. Care might be indicated for patients receiving aspirin and PGAGs because of the potential for increased bleeding times. Coagulation times are prolonged only after a large dose, and peak effect occurs at approximately 7 hours after treatment. Surgical

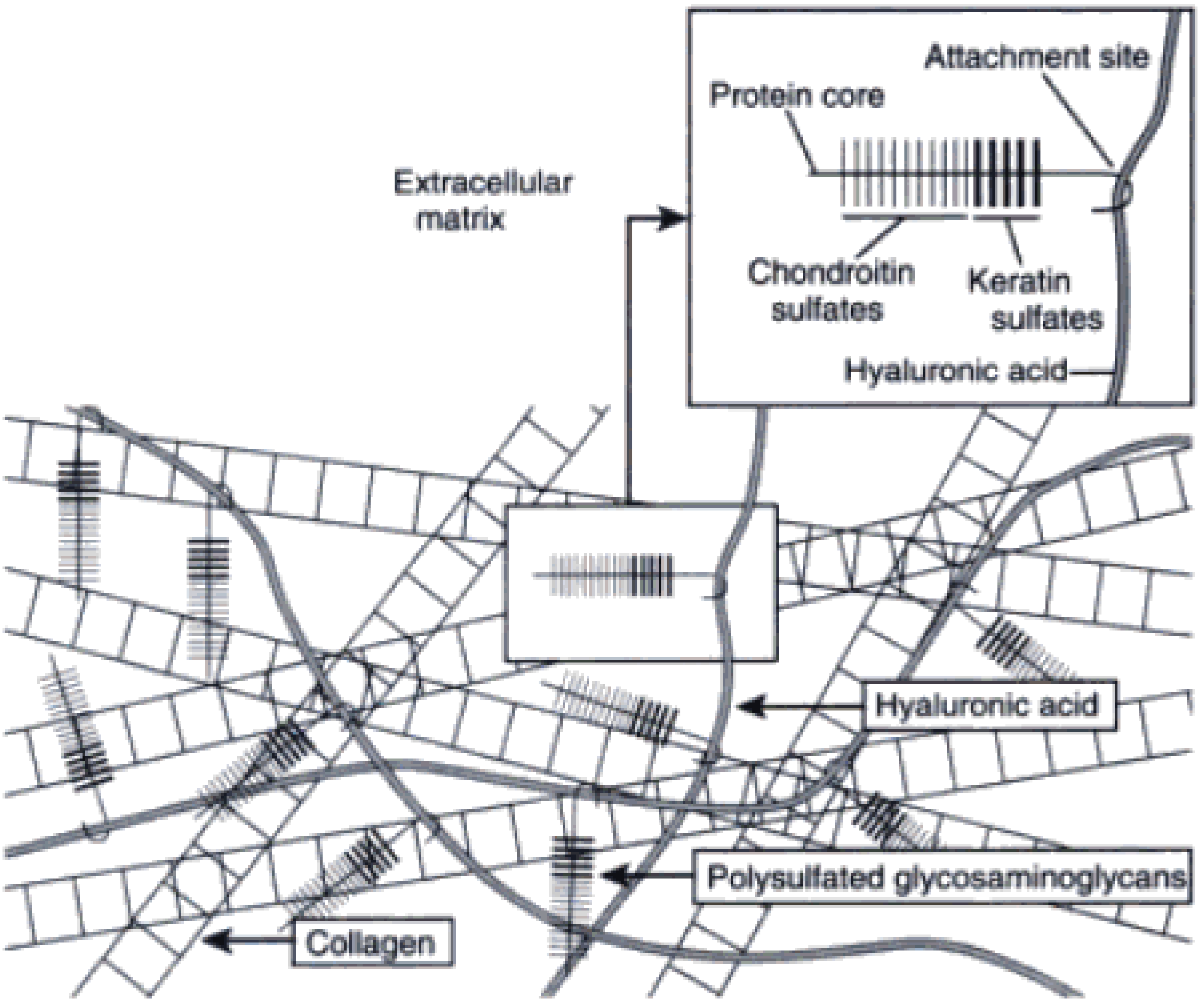


Figure 16–7. Hyaline articular cartilage is characterized by highly metabolic chondrocytes surrounded by an extracellular matrix that they secrete *(inset, top left)*. The matrix is composed of collagen, which provides strength to the joint, and polysulfated glycosaminoglycans (PGAGs). The PGAGs cause retention of water, thus providing a cushion to joint stresses. The PGAGs are composed of a central protein core *(inset, top right)* to which is attached keratin sulfates (base) and chondroitin sulfates. The PGAG attaches to hyaluronic acid.

candidates probably should not be treated with adequan on the day of surgery.

Pentosan Polysulfate

Pentosan polysulfate (PPS) is isolated from beechwood hemicellulose and synthetically modified by adding sulfates to its repeating units of xylanpyranoses. Thus, unlike adequan, it is not derived from animal sources. It is available as an injectable product, and an oral product has been recently approved in the United States for people with interstitial cystitis, a syndrome that may reflect a quantitative and qualitative defect in bladder mucosal glycosaminoglycans (Jepsen et al., 1998; Barrington and Stephenson, 1997). Response of interstitial cystitis (based on resolution of pain) ranges from 6 to 20%. In Europe, PPS is used to treat thrombosis and hyperlipidemia, with application for treatment of osteoarthritis being only recent. It may improve subchondral and synovial membrane blood flow. In addition, it modulates cytokine actions, stimulates hyaluronic acid synthesis, and maintains PGAG content in joints (Nethery et al., 1992; Ghosh and Hutadilok, 1996). When PPS was administered intramuscularly (2 mg/kg once weekly) in a model of osteoarthritis in dogs, cartilage damage was significantly decreased. In a double-blind clinical trial in 40 dogs, after 3 mg/kg intramuscularly per week, lameness, body condition, pain on joint manipulation, and willingness to exercise were improved at 4 weeks (Read et al., 1996). An oral dose has not been established for dogs. The drug appears to be safe, but like other PGAG-like compounds, it appears to prolong clotting times and may cause thrombocytopenia. The use of this product for syndromes other than osteoarthritis in humans (including interstitial cystitis, thrombosis, and so forth) potentially might lead to similar uses in animals. For example, a study of mouse mesangial cells found that PPS decreased proliferation and net extracellular matrix production, mechanisms that may explain its apparent ability to slow the progression of glomerular sclerosis (Elliot et al., 1999; Striker et al., 1997). Pentosan polysulfate inhibits calcium oxalate crystallization in vitro (Senthil and Malini, 1998) and is being studied for possible use in vivo. The compound is being studied for its apparently clinically beneficial effects for the treatment of AIDS-related Kaposi's sarcoma in human patients (Schwatsmann et al., 1996).

Hyaluronic Acid

Hyaluronic acid is a linear polydisaccharide (glucuronic acid combined with glucosamine) that is an essential component of synovial fluid, where it is chemically linked to proteoglycans in articular cartilage. As such, it helps to form large, aggregating proteoglycans in articular cartilage (Pinals, 1992). Its mode of action is not certain, but it is assumed to function as a lubricant by increasing viscosity of synovial fluid. It may also act as an anti-inflammatory. Studies in horses support its efficacy in the treatment of osteoarthritis. After intra-articular injection, the drug persists in joints for several days. The drug also has been given intravenously; the half-life in horses is 96 hours, but the drug has not been studied in dogs. Hyaluronic acid exists in variable molecular weights. High-molecular-weight hyaluronic acid inhibits phagocytosis, lymphocyte migration, and synovial permeability and stimulates hyaluronic acid synthesis (Tobin, 1979). Prior treatment with glucocorticosteroids or bony changes limits response. Hyaluronic acid appears to be very safe; side effects tend to be associated with administration of the drug. The drug has been used with variable success after intra-articular injection in horses (Asheim and Lindblad, 1976) and dogs (Campos, 1998).

Oral Disease-Modifying Agents

Veterinary Nutraceuticals

The use of oral disease-modifying agents (slow-acting disease-modifying agents; Anderson, 1999a, b) for the treatment of damaged joints remains controversial but is becoming increasingly accepted. Currently, with the exception of oral PPS, these products can be classified as veterinary nutraceuticals (Anderson, 1999a, b; Boothe, 1997a, b). The North American Veterinary Nutraceutical Council has defined a veterinary nutraceutical as "a [non-drug] substance which is produced in a purified or extracted form and administered orally to a patient to provide agents required for normal body structure and function and administered with the intent of improving the health and well-being of animals (Boothe 1997a, b)."

It is important to note that these products fall under no regulatory agency, and as such neither safety nor efficacy has necessarily been documented before they were marketed. Those companies that provide efficacy and safety data have done so voluntarily, suggesting a level of credibility that may not be present with "me also" products. An exception occurs for those states that follow the American Association of Feed Company Organization (AAFCO) guidelines for state marketing of products added to feeds. Because these compounds do not fall under the definition of food or drugs as defined by the Food and Drug Act, AAFCO considers them to be feed or feed additives and thus under their jurisdiction. AAFCO is presently generating guidelines regarding the sale of veterinary nutraceuticals, and state regulations will vary until that time. The Center for Veterinary Medicine currently does not plan to regulate these products, nor does it play to apply regulations for human dietary supplements (as defined by the Dietary Supplement Health and Education Act of 1994) to veterinary products. Regardless of the regulatory status of veterinary products, until the FDA implements regulatory guidelines for human products, human products can be accessed by pet owners through health food and other stores. However, for both human and veterinary products, neither safety nor efficacy should be assumed.

Currently, the label of a nutraceutical (or any) product cannot contain terminology that implies a therapeutic intent. The inclusion of a medical claim (or correction of a medical deficiency) without the presence of an FDA new animal drug approval (NADA) number on the label indicates that the product is an unapproved drug. The lack of an NADA suggests that efficacy and safety studies of the compound are probably not available (Boothe, 1997a, b); however, some manufacturers will assume a proactive role in establishing the efficacy of these compounds. The FDA may not regulate products with a medical claim but no NADA simply because its limited resources may be reserved for more important issues. Unfortunately, clients may not realize the lack of regulation of these products, and counseling by veterinarians may be important.

On the other hand, the lack of efficacy data should not lead to the classification of these compounds as "quackery." Establishing efficacy for these products may be very difficult because of the complex nature of their actions and the dependence of their actions on other endogenous molecules (Boothe, 1997b). Safety may be more easily established and should be established before the use of any of these products. Harm may occur not only because of the compounds themselves but also because of possible contaminants. Additional harm may occur if the client neglects traditional therapies in the belief that the nutraceutical agent will be sufficiently effective. Studies sponsored by industry or academia for a number of these products have provided evidence of efficacy.

Several products have been used by many veterinarians or pet owners with evidence of benefit and minimal side effects (Anderson et al., 1999). Veterinarians should establish whether the product has been manufactured according to good manufacturing practices. The label should include the exact amount of each active ingredient; labels that combine metric and apothecary systems may be intentionally misleading because conclusions regarding product content are more difficult to determine. Each product listed on the label should contain a specific dosage. The source of each compound should be noted on the label. Note that products based on whole body tissues (mussel-containing glycosaminoglycans) will lack milligram contents of specific compounds (chondroitin sulfate). When individual products are listed, the purity of the compounds is likely to vary among and within products. The stated purity may not be the actual purity, particularly if good manufacturing procedures are not followed. Anderson (1999b) notes that 70% of products analyzed for glucosamine and chondroitin sulfate did not meet the labeled claims.

Nutraceutical Disease–Modifying Agents

Nutraceutical products that target osteoarthritis contain various forms of glycosaminoglycans or their component parts (aggregates form proteoglycans, the major constituent of cartilage matrix), such as glucosamines or chondroitin sulfates, appear most promising for treatment of osteoarthritis based on studies that have supported their efficacy (Hanson, 1996; Hanson et al., 1997; White et al., 1996; Anderson and Slater, 1997; Bucci, 1994; McNamara et al., 1997; Phillipi, 1999; McCarty, 1998; Barclay, 1998) and safety (McNamara et al., 1996). Presumably, as precursor nutrients, chondroitin sulfates, glucosamines, and other ingredients that comprise these will be extracted from the serum by chondrocytes and used to synthesize proteoglycans. During periods in which cartilage degradation exceeds cartilage formation, the need for precursor molecules may exceed availability, and the repair process is inhibited. The availability of orally administered compounds not only increases the efficiency of the ability of the chondrocytes to repair damaged cartilage, as is evidenced by increased synthesis, but also leaves less opportunity for formation of inappropriate molecules.

Glucosamine

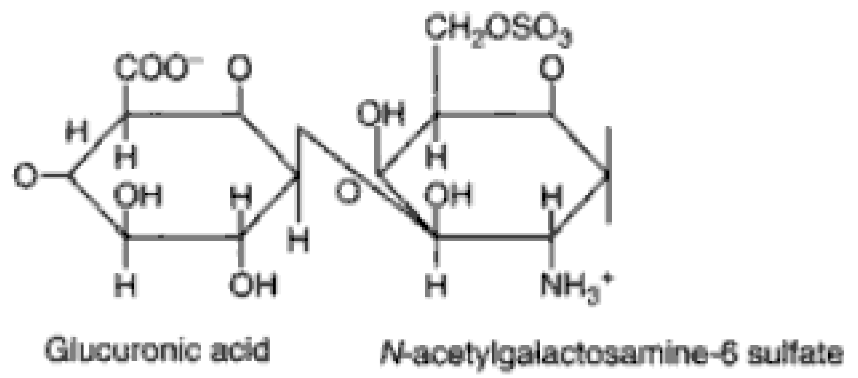
Glucosamine is an amino sugar that appears to be important in chondrocyte synthesis of PGAG. A deficiency of the compound has been implicated as a cause of decreased PGAG synthesis in early osteoarthritis. Alternatively, glucosamine also may stimulate synovial production of hyaluronic acid (McCarty, 1998). Its use in the treatment of osteoarthritis remains controversial despite in vitro and in vivo studies supporting its efficacy in improving lameness scores and mobility in human and animal models of DJD. Some of the controversy probably reflects poor design of selected clinical trials (Barclay, 1998). After meta-analysis of studies on glucosamine, it can be concluded that, in humans, the compound is well absorbed after oral administration; first-pass metabolism due to incorporation into proteins reduced oral bioavailability to 26% (Barclay, 1998). Unbound glucosamine is incorporated into articular cartilage.

Several glucosamine salts are available, including sulfate, hydrochloride, and hydroiodide. All appear to be equally well absorbed and equally effective (Bucci, 1994), although one in vitro study suggests that the *N*-acetyl salt may be less efficacious. Glucosamine sulfate kinetics has been studied in dogs (Setnikar et al., 1984). After oral administration, absorption was rapid and nearly complete (87%). The compound is bound (by the liver) to plasma globulins. In humans, a dose of 1 g daily has been recommended. Galactosamine salts (also found in PGAGs) and glucuronide salts do not appear to be effective in damaged joints (Bucci, 1994).

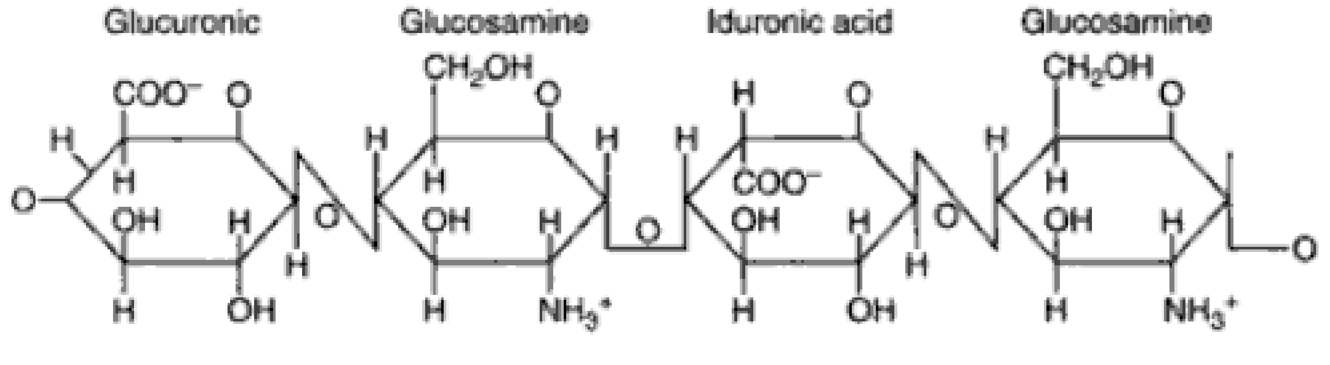
Chondroitin Sulfate

Chondroitin sulfates are glycosaminoglycans (repeating units of galactosamine sulfate and glucuronic acid) that can be found in many tissues (Fig. 16–8). In cartilage matrix, they bind to and support collagen. Differences in molecular weight result in variable oral bioavailability. Chondroitin 4-sulfate is mammalian in origin, and it is the most abundant chondroitin in growing mammalian cartilage. With age, chondrocyte secretion of chondroitin 4-sulfate may decline, contributing to the initiation of DJD. Chondroitin 6-sulfate is derived from shark cartilage and conceptually may be less ideal than chondroitin 4-sulfate. Chondroitin sulfates appear not only to increase synthesis of PGAGs but also to competitively inhibit the actions of metalloproteases in cartilage matrix. They have a variety of other in vitro and in vivo effects on cartilage. In humans (dosed at 1 to 1.5 g/day), they decrease the need for NSAIDs.

Despite its large molecular size, 70% of chondroitin sulfate is absorbed in various sizes ranging from intact chains to monomer subunits after oral administration. The presence of chondroitinases found in carnivorous and omnivorous animals has been postulated as the reason for absorption (Bucci, 1994). In dogs, oral chondroitin increases serum glycosaminoglycans. Because of its ubiquitous location in the body, indications other than joint disease should be considered for chondroitin sulfates,



CHONDROITIN 6-SULFATE



HEPARIN

Figure 16–8. Chondroitin sulfates structurally are very similar to heparin and hyaluronic acid (not shown). The negative charges of the repeating units cause retention of water. Inappropriate chemical configuration of the chondroitin sulfates contributes to abnormal stresses on the joint and ultimately continued articular damage.

including cardiovascular diseases associated with thrombogenesis and indications previously noted for PPS. Attention should be paid to the source of chondroitin sulfates in nutraceuticals. Purified preparations are expensive, but the amount of chondroitin in whole animal tissues (mussel, shark cartilage, sea cucumber, or sea algae) cannot be determined from the label. Bioavailability of the chondroitin sulfates in such products is not known.

Miscellaneous

Variable other ingredients can be found in oral nutraceutical compounds intended for the treatment of osteoarthritis. Manganese is found in some oral disease–modifying agents. It is an essential trace element and cofactor for the synthesis of glycosaminoglycans. Ascorbic acid, a component of Cosequin, a veterinary disease-modifying agent (and its human counterpart, Cosamine) is a reducing agent for enzymes that form residues important for fibril formation and cross-linkage of collagen fibers for the articular cartilage, joint capsule, tendons, ligaments, and bone. In addition to combined products of pure ingredients, several products composed of cartilage or mucopolysaccharide mixtures are available. Shark cartilage has a low percentage of glycosaminoglycans. Although a few anectodal reports may support its efficacy, scientific support is not available. Perna mussel is a reported yet undocumented source of glycosaminogycans; listed constituents include fats, proteins, amino acids, enzymes, and carbohydrates.

The therapeutic use of these compounds is just being established. Although evidence of efficacy of combination products has been lacking (Kelly, 1998), scientific studies using animal models and spontaneous causes of osteoarthritis in dogs are increasingly supporting their use in osteoarthritis (Fig. 16–9). Anderson (1999a, b) has reviewed studies supporting both the efficacy and safety of combination products in dogs and cats.

The compounds might be considered as "follow-up" for patients that have responded to PGAGs. As with injectable PGAG agents, however, they should be considered for any condition in which joint damage is suspected or anticipated, including trauma, overuse, surgery, or infections or immune-mediated causes. Combination therapy with various products (including NSAIDs) should be considered. Because a number of these products might protect against NSAID-induced chondrodestruction, combined use of PGAGs or Cosequin or similar products should be considered. The use of combinations that provide different mechanisms of action (or different targets of supplementation) should also be considered. Finally, these products might be used before the onset of clinical signs (or radiographic evidence) of osteoarthritis in patients predisposed to develop orthopedic maladies.

S-Adenosylmethionine

S-Adenosylmethionine (SAMe) also is a nutraceutical product, but, unlike the previously discussed products, its mechanism for treatment of OA is less clear and probably reflects anti-inflammatory effects. It is synthesized in the body from methionine and is responsible for a number of biologic reactions, serving as a methyl donor. In the joint, it may act to transulfate glycosaminoglycans. Its precursor (methionine) cannot be administered during states of deficiency without avoiding toxicity. The product must be prepared as a salt because it is unstable; it is extremely hygroscopic, and the tablet cannot be broken without loss of efficacy. In human clinical trials (controlled and uncontrolled), SAMe has improved lameness scores and mobility. In vitro studies suggest that SAMe increases proteoglycan synthesis as well as protecting the cartilage (Anderson, 1999a). This is being studied in dogs. The human dose is 600 mg/day for the first 2 weeks, followed by 400 mg/day. Clinical response may not be evident for 1 or 2 months.

OTHER ANTI-INFLAMMATORY DRUGS

Orgotein

Orgotein, or superoxide dismutase, is a copper- and zinc-containing metolloprotein that can be an effective anti-

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Figure 16–9. Histologic evidence of the clinical efficacy of disease-modifying agents. A surgically-induced instability model of osteoarthritis was induced in rabbits. Treated rabbits received 0.38 g glucosamine HCl and 0.304 g sodium chondroitin sulfate (Cosequin, Nutramax Laboratories, Inc., Edgewood, MD) per kilogram body weight per day. Histologic samples were collected at 16 weeks from the center of the medial condyle. Differences in lesions between the groups were significant ($p < 0.02$). (Photographs provided courtesy of Nutramax Laboratories.)

inflammatory. As an endogenous intracellular enzyme, it occurs at very low concentrations in many tissues, but particularly the liver, where it scavenges tissue-damaging oxygen radicals. Phagocytic cells (neutrophils and macrophages) generate large amounts of cytotoxic superoxides during the inflammatory process. Among the radicals apparently scavenged by orgotein is peroxynitrite, a long-lasting radical that can contribute to chondrocyte death (Anderson, 1999a). The half-life of phagocytic cells is prolonged in the presence of superoxide dismutase (Salin and McCord, 1975; Tobin, 1979). Approximately 2 to 6 weeks of therapy may be required before therapeutic benefits are realized.

Orgotein is characterized by a wide margin of safety, with the lethal dose being over 40,000 times the therapeutic dose. As a large molecule, efficacy via any route other than intra-articular is questionable due to poor absorption. The drug has, however, also been administered clinically both intramuscularly and orally (Breshears et al., 1974). Absorption of the oral preparation has not been documented. Molecular size limits renal elimination of the drug. After intra-articular administration, orgotein was 94% effective in horses lame for less than 2 months compared with only 49% in horses lame for longer than 2 months before treatment (Ahlengard et al., 1978). The use of orgotein in combination with disease-modifying agents is a rational approach for control of inflammation; however, other anti-inflammatories may be necessary to effectively control inflammation.

Dimethylsulfoxide

Dimethylsulfoxide (DMSO) is a hygroscopic solvent derived from wood pulp. It is used as a drug vehicle because of its ability to dissolve drugs not soluble in water. Because of its discreet chemical characteristics, DMSO is variably categorized (Brayton, 1986; Alsup, 1984).

Pharmacologic Effects

As an anti-inflammatory, DMSO is a scavenger of free oxygen radicals. Anti-inflammatory effects have been reported in acute musculoskeletal injuries and central nervous inflammatory processes and after trauma (Wong and Reinertson, 1984; Spitzer, 1991). Chronic diseases are less responsive to the anti-inflammatory effects of DMSO. Immunomodulation may be responsible for some of the anti-inflammatory effects of DMSO. The drug inhibits white blood cell migration and antibody production. Fibroblast proliferation is also inhibited. The analgesic effects of DMSO have been compared with those of narcotic analgesics. Analgesia has been reported in a variety of situations, including acute and chronic musculoskeletal disorders and postoperative pain. Although nerve blockade has been reported in vitro, it is unlikely that concentrations occur in vivo sufficient to effect this response. Opiate receptors also do not seem to be involved. Other pharmacologic effects include inhibition or stimulation of enzymes, vasodilation (due to histamine release), inhibition of platelet aggregation, radioprotection, cryopreservation, and antimicrobial (antifungal, bacterial, and viral) activity (Wong and Reinertson, 1984; Brayton, 1986). Diuresis occurs after topical, oral, or parenteral administration, probably due to its hygroscopic nature and ability to pull water into the tubules. Dimethylsulfoxide (3.0 mg/kg in 20% solution) has been reported to protect the kidneys against ischemic insults. A sedative effect has also been reported in several species (Brayton, 1986).

Disposition

After oral administration of 1 g/kg, peak plasma drug concentrations occur within 4 to 6 hours, and detectable levels persist in the plasma for 400 hours (Wong and Reinertson, 1984). Within 20 minutes of topical application, DMSO penetrates the skin and can be detected in all organs of the body (Brayton, 1986). Peak plasma drug concentrations occur 2 hours after topical administration (Wong and Reinertson, 1984). Its ability to penetrate the skin is believed to reflect exchange and interchange with water in biologic membranes. Mucous membranes, lipid membranes of cells and organelles, and the blood-brain barrier are similarly penetrated without irreversible membrane damage (Brayton, 1986). Tooth enamel and keratin appear to be the only tissues that DMSO does not penetrate (Wong and Reinertson, 1984). Dimethylsulfoxide facilitates penetration of other substances across membranes; cutaneous penetration of steroids, sulfadiazine, phenylbutazone, and other drugs has been documented (Brayton, 1986; Alsup, 1984). Enhanced absorption of therapeutic drugs can lead to toxicity, particularly for anesthetic, cardioactive, and anticholinesterase drugs.

Dimethylsulfoxide is partially metabolized by hepatic microsomal enzymes (Brayton, 1986), but the primary route of elimination appears to be in the urine as the parent compound (Wong and Reinertson, 1984). Although a significant amount of DMSO may be eliminated in the bile, most undergoes enterohepatic circulation (Wong and Reinertson, 1984). Hepatic metabolism of a small amount of DMSO (3 to 6%) to dimethylsulfide and subsequent pulmonary excretion of this metabolite accounts for the halitosis that occurs regardless of the route of administration (Wong and Reinertson, 1984).

Adverse Effects

Dimethylsulfoxide is characterized by a large safety margin. Signs associated with near lethal IV doses include sedation, diuresis, intravascular hemolysis, and hematuria. Death is preceded by hypotension, prostration, convulsions, and respiratory distress characterized by dyspnea, tachypnea, and pulmonary edema. Phlebitis and venous obstruction may occur with IV dosing. Intravascular hemolysis is concentration and rate dependent, and concentrations less than 10% are recommended for IV administration. Susceptibility to hemolysis will vary with species due to differences in erythrocyte fragility. Nephrotoxicity has been reported in some species. Necropsy lesions include hematuria, hemoglobinuria, and mild tubular nephrosis. Chronic toxicity studies in laboratory animals have documented hepatotoxicity, which may be due to its metabolism by the liver to toxic metabolites. Dimethylsulfoxide may also enhance hepatotoxicity of other drugs as well as hepatic binding and metabolism of selected carcinogens.

Teratogenicity has also been reported in some animals. Ocular toxicity occurs with daily, long-term administration and develops more rapidly in young animals. Lesions occur in the lens and appear as altered lucency, making animals myopic. Histologic abnormalities are not apparent. Such a response was reported in one horse that received 0.6 g/kg daily cutaneously for 2 months. Skin reactions are common, particularly at higher concentrations, and are manifested as erythema, warmth, and local vasodilation. A wheal and flare response and pruritus may also occur. Repeated application may result in drying and desquamation of the epithelium (Brayton, 1986).

Clinical Use

Dimethylsulfoxide is approved for topical application in horses suffering from acute swelling due to trauma and in the treatment of acute or chronic otitis. In humans, DMSO is approved for interstitial cystitis. Although not approved, DMSO has been recommended for therapy in male cats suffering from urinary tract obstruction (Brayton, 1986). Other reported applications of DMSO include facilitation of healing of skin wounds (including habronemiasis of horses), acral lick dermatitis in dogs, postoperative fibrous adhesions, acute CNS trauma, inflammation, edema or ischemia, intervertebral disk disease, fibrocartilaginous embolization, ischemic insults, postoperative myositis, rheumatic diseases, myasthenia gravis, and chronic musculoskeletal conditions. Dimethylsulfoxide also inhibits alcohol dehydrogenase and thus has been recommended for the treatment of ethylene glycol toxicity (Brayton, 1986).

Methylsulfonylmethane

Methylsulfonylmethane is a naturally occurring metabolite of DMSO that has also received attention as a food additive for control of musculoskeletal inflammation. Few data are available to support the use of this compound for therapy of osteoarthritis.

Pentoxifylline

Pentoxifylline is a methylxanthine derivative of theobromine with minimal bronchodilator activity but with clinically apparent rheologic effects (Serafin, 1996). It is used to treat human patients with claudication associated with chronic occlusive arterial disease. Mechanisms do not include vasodilation or cardiac stimulatory effects. Its rheologic effects appear to reflect increased flexibility of red blood cells and reduced blood viscosity (Ambrus et al., 1990). Its disposition is complex, with hepatic metabolism to at least seven metabolites, two of which (I and V) are responsible for most of the pharmacologic effects (Ambrus et al., 1995). The drug has been used to treat collie dermatomyositis (Chapter 33). Animals benefit from both the rheologic effects and the apparent anti-inflammatory effects of this drug. Pentoxifylline inhibits the complement cascade, neutrophil adherence, and cytokine production.

In human patients, inflammatory conditions for which pentoxifylline has been used have included contact dermatitis, systemic vasculitis, and sepsis syndromes (Serafin, 1996). The disposition of the drug has been studied in normal dogs (Rees, 1999). After a dose of 30 mg/kg oral and 8 mg/kg IV (n = 5 dogs), pentoxifylline and its metabolites are characterized by an elimination half-life of 125 ± 192 and 450 ± 533 minutes, respectively, suggesting slow absorption. Peak concentrations were 41 ± 46 and 40 ± 32 μg/mL for IV and oral administration, respectively. Bioavailability was 76 ± 78%. No side effects occurred in any dog at this dose. Although therapeutic concentrations have been recommended in humans, this is based on the parent compound. However, therapeutic ranges should be based on both the parent drug and its most active metabolites. The drug currently is being studied in the treatment of collie dermatomyositis.

USE OF MODULATORS OF INFLAMMATION IN THE TREATMENT OF SHOCK AND CENTRAL NERVOUS SYSTEM TRAUMA

A number of drugs that modulate the inflammatory response have been studied for their effect in the patient suffering from shock, particularly that associated with the release of bacterial toxins such as endotoxin (septic shock). Because of the oxygen radical scavenging ability of some of these drugs, studies have also focused on their use for treatment of damage to the CNS.

Pathophysiology of Septic Shock

The lipid A component of lipopolysaccharide (LPS), endotoxin, found on the surface of gram-negative organisms is a highly conserved molecule responsible for the sequelae of endotoxic shock. The manifestation begins as endotoxin released from dying gram-negative organisms interacts with receptors on cell of the hosts defense system: macrophages, neutrophils, platelets, and lymphocytes. Endotoxin also directly interacts with vascular endothelial cells. In response, cells either release the mediators of endotoxic shock or render other cells more reactive to cellular signals and subsequent mediator release. Mediators of endotoxic shock are grouped as cytokines, lipid mediators, or secondary mediators (Olson et al., 1995; Whittle, 1995). Cytokines are small polypeptides released from inflammatory cells, especially macrophages. Tumor necrosis factor and IL-1 are the two cytokines that appear to be primarily responsible for the cascade of endotoxemia (see Fig. 10–3). Their effects in turn are often mediated by nitric oxide. Lipid mediators are derived from AA, located in the phospholipids of cell membranes, particularly those of neutrophils, platelets, vascular endothelium, and vascular smooth muscle. Examples include prostaglandins (including thromboxane), leukotrienes, and platelet-activating factor.

Both cytokines and the lipid mediators act as signaling mechanisms between inflammatory cells, platelets, and the vascular endothelium through negative and positive feedback mechanisms. When the positive feedback loops overwhelm the negative feedback loops, the pathophysiology of endotoxic shock becomes a clinical reality. The pathophysiology reflects, in part, the direct effects of endotoxin (e.g., it directs activation of Hageman factor and complement components) and the combined or individual effects of the mediators. Secondary mediators (such as histamine, serotonin, vasopressin, angiotensin II, catecholamines, and opioids) are released in response to cytokines and lipid mediators, resulting in the general signs of endotoxic shock.

Changes in peripheral vasculature (i.e., constriction and dilation), activation of clotting factors, and vascular endothelial damage occur. The clinical signs associated with each stage of shock depend on the mediators released during that stage and vary among species. The complex interactions of these mediators, however, if allowed to progress, can result in multiple organ failure in any species simply because of the cumulative effects of hypoxia: oxygen radical, lysosomal enzymes, thrombosis, and metabolic derangements. Drug therapy is most likely to be successful when initiated early during the course of endotoxic shock. A number of steroidal compounds have been studied for their efficacy (Howe, 1998).

Role of Lipid Peroxidation in Tissue Injury

Lipid peroxide formation is the result of free radical–mediated cell and tissue injury caused by lipid peroxides within cell membranes and organelles. Both structure and function of the membranes and organelles are disrupted by lipid peroxide formation. Lipid peroxidation is a potentially geometrically progressing reaction that spreads over the surface of cell membranes, impairing phospholipid-dependent enzymes, ionic gradients across the cell membrane, and, if sufficiently severe, membrane lysis (Fig. 16–10). Its importance, along with the generation of oxygen radicals, is evident early in the pathophysiology of CNS trauma. Lipid peroxidation is only one of several sources of oxygen radial formation; other sources include the AA cascade, catecholamine oxidation, mitochondrial "leak," oxidation of extravasated hemoglobin, and, as the inflammatory process proceeds, infiltrating neutrophils.

Lipid peroxidation is initiated by a reactive oxygen molecule. After CNS trauma, the generation of oxygen radicals during the normal reduction of oxygen overwhelms normal control mechanisms. Xanthine/xanthine oxidase, prostaglandin synthetase, and other mechanisms result in superoxide anion formation. Although superoxide anion is not in and of itself very reactive, it becomes more so by accepting a proton, thereby becoming more able to penetrate cell membranes. Other sources of superoxide anion include catecholamines; ascorbic acid and glutathione act to inhibit superoxide anion. The superoxide anion can also

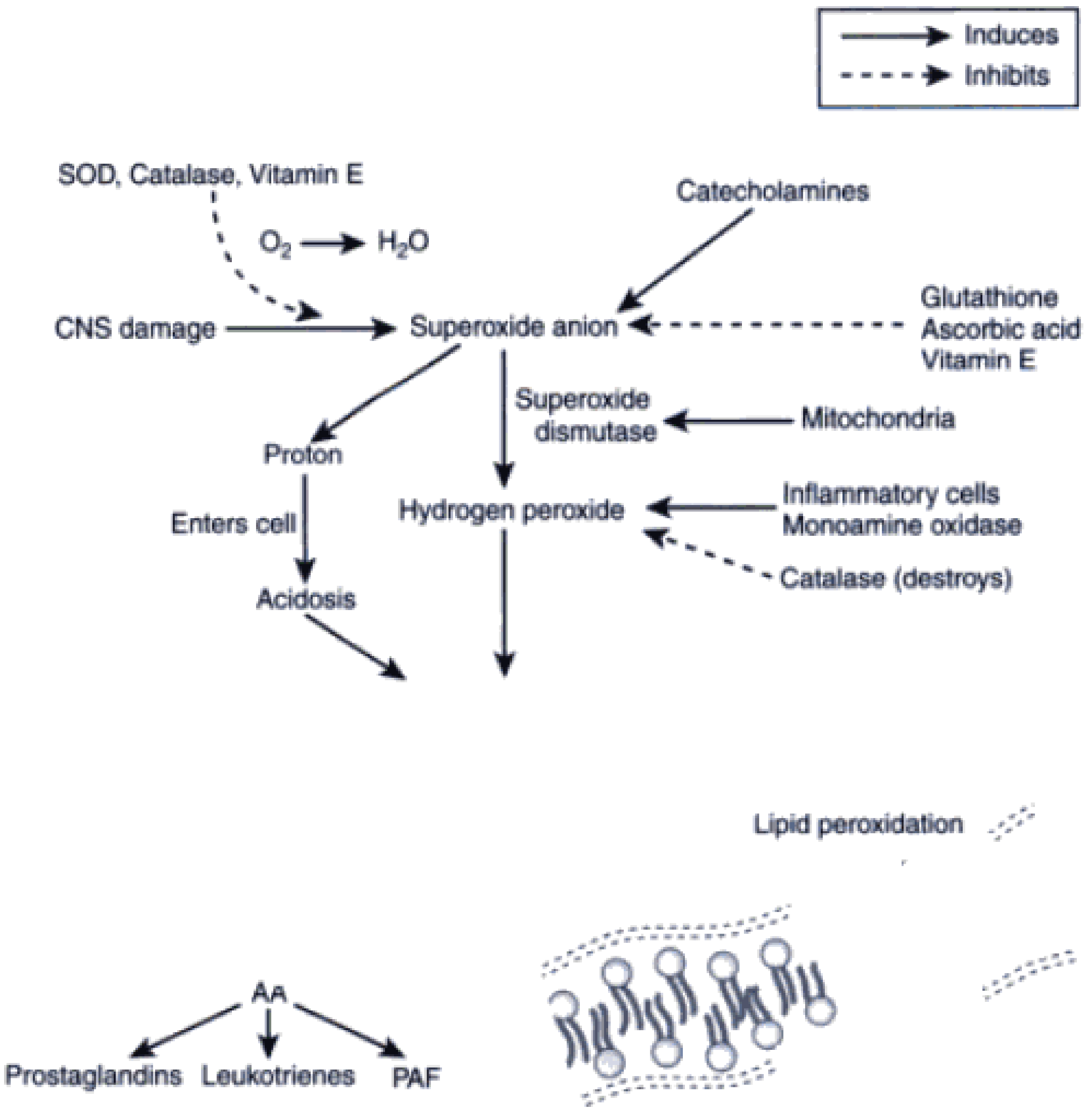


Figure 16–10. Lipid peroxidation of cell membranes reflects a cascade of events that begins with neurologic damage. Oxygen radical formation is potentiated in the presence of iron and is inhibited by endogenous protectants such as superoxide dismutase (SOD, which converts the superoxide radical to hydrogen peroxide) and catalase. Catecholamine release can contribute to damage. The ability of the radicals to move down the cell membrane is facilitated by the fluidity of the membrane. Calcium influx accompanying cell membrane damage contributes to the formation of arachidonic acid metabolites and subsequent inflammation. AA = arachidonic acid; CNS = central nervous system; PAF = platelet activating factor.

become more dangerous by conversion via superoxide dismutase to hydrogen peroxide. Inflammatory cells are an important source of hydrogen peroxide, as is degradation of monoamines mediated by monoamine oxidase. Mitochondria contain high concentrations of superoxide dismutase. Although hydrogen peroxide also is not very damaging to tissues, it can easily penetrate cell membranes unless destroyed first by catalase. In the cell membrane, hydrogen peroxide interacts with iron to yield the highly reactive hydroxyl radical.

Normally, the conversion of oxygen to water is well controlled by the presence of superoxide dismutase, catalase, and endogenous antioxidants, with vitamin E being one of the most important membrane-bound antioxidants. After CNS trauma, normal control mechanisms are lost, and lipid peroxidase formation begins. Iron plays a crucial role in this process. Free iron released from hemoglobin, transferrin, or ferritin in the presence of a lowered tissue pH or oxygen radicals catalyzes radical-initiated peroxidation (see Fig. 16–10). Iron/oxygen complexes probably initiate lipid peroxidase formation; damage during ischemic injury from radicals will be affected by the amount and location of iron (and copper) ions. Unfortunately, these ions become more available during injury. Acidosis, which often accompanies ischemia (anaerobic environment and lactic acidosis), increases the solubility of iron. Free calcium released during the injury stimulates phosopholipase A_2 and the AA cascade. Metabolites of AA are important sources of reactive oxygen species. Inflammatory cells become an important source of continued AA metabolism. Decreased concentrations of vitamin E, ascorbic acid, and glutathione (induced by scavenging of oxygen radicals) predicate the occurrence of lipid peroxidation.

Drugs that Impair Lipid Mediators

Nonsteroidal Anti-inflammatory Drugs

A number of NSAIDs have been studied for their ability to block response to mediators of endotoxic shock. Indomethacin and ibuprofen have shown efficacy in human patients (Kettelhut et al., 1987). Flunixin meglumine has been studied in horses and dogs (Shuster et al., 1997; Hardie et al., 1983). As with glucocorticoids, however, the effects of NSAIDs must be realized within the first 2 hours of the onset of endotoxic shock—that is, before mediators have been able to stimulate response. The use of NSAIDs may shunt AA substrate to the lipoxygenase pathway, which may cause detrimental effects. Thus, drugs that impair both arms of the AA cascade may prove more useful. The efficacy of ketoprofen, an NSAID that appears to inhibit both prostaglandins and leukotrienes, has been shown to ameliorate many of the effects of endotoxin infusion (Sigurdsson and Youssef, 1994). The combined use of NSAIDs with leukotriene antagonists apparently has not been reported in endotoxic shock. Prolonged therapy with NSAIDs should be avoided because of toxic effects. Although gastrointestinal toxicity is the major concern in most animals, the patient suffering from endotoxic shock may be more predisposed.

Glucocorticoids

Glucocorticoids are discussed in Chapter 17. Glucocorticoids inhibit the enzyme phospholipase A_2 and the release of TNF and IL-2 from activated macrophages (Boumpas et al., 1993). Glucocorticoids also alter synthesis of and biologic response to collagenase, lipase, and plasminogen activator. The immunosuppressive actions of glucocorticoids are more pronounced on the cellular arm than the humoral arm of the immune system. Glucocorticoids have minimal effects on plasma immunoglobulin concentrations, but can modulate immunoglobulin function. Immunosuppressive actions of glucocorticoids, like their anti-inflammatory actions, involve disruption of intercellular communication of leukocytes via interference with lymphokine production and biologic action. Glucocorticoids block the effects of macrophage-inhibiting factor and interferon-γ (IFN-γ) on macrophages. IFN-γ, which is released from activated T cells, plays an important role in facilitating antigen processing by macrophages. Glucocorticoids inhibit the synthesis and release of IL-1 by macrophages, thereby suppressing the activation of T cells. Glucocorticoids also inhibit IL-2 synthesis by activated T cells. Interleukin-2 plays a critical role in amplification of cell-mediated immunity. Additionally, glucocorticoids suppress the bactericidal and fungicidal actions of macrophages.

Septic Shock Experimental models of septic shock have shown glucocorticoids to be of benefit if administered before or concurrently with endotoxin administration—that is, within the first 2 hours. In canine models, severe mesenteric vasoconstriction within the first 15 minutes can lead to irreversible shock. Thus, it is important to note that glucocorticoids provided no beneficial effects when they were administered 30 to 60 minutes after administration of the endotoxin. Clinically, the likelihood of knowing the time of onset of endotoxemia or sepsis is extremely low. Rapid-acting, water-soluble agents such as dexamethasone sodium phosphate (4 to 8 mg/kg, IV), prednisolone sodium succinate or sodium phosphate (30 mg/kg, IV), or methylprednisolone sodium succinate (30 mg/kg, IV) are preferred if glucocorticoids are to be used. Shock doses of glucocorticoids are 5 to 10 times the immunosuppressive dose. Glucocorticoids should not be used indiscriminately for treatment of septic shock. In human patients, their use is controversial, with no improvement in survival in some studies (Bone et al., 1987) (see Chapter 17). Indeed, mortality was greater in one study, presumably due to immunosuppression and secondary infection.

Hemorrhagic Shock The use of glucocorticoids for treatment of hemorrhagic shock is controversial. Some studies in dogs suggest that dexamethasone sodium phosphate (5 mg/kg, IV) may improve blood flow to the kidneys, lungs, and gastrointestinal tract. Other supportive measures, particularly aggressive fluid therapy, must also be instituted. Appropriate fluid replacement therapy will ensure adequate drug distribution to target tissues.

Oxygen Radical Scavengers In the last decades, a neuroprotective role has been recognized for select glucocorticoids and, most notably, methylprednisolone. Interest stemmed from the observation that the ability to inhibit CNS lipid peroxidation and influence other pathophysiologic processes strongly correlated with neurologic recovery. More recently, the neuroprotective effects have been separated from the glucocorticoid activity by the discovery of nonglucocorticoid steroids that are able to equal or surpass the antioxidant effects of methylprednisolone (see later discussion of lazaroids).

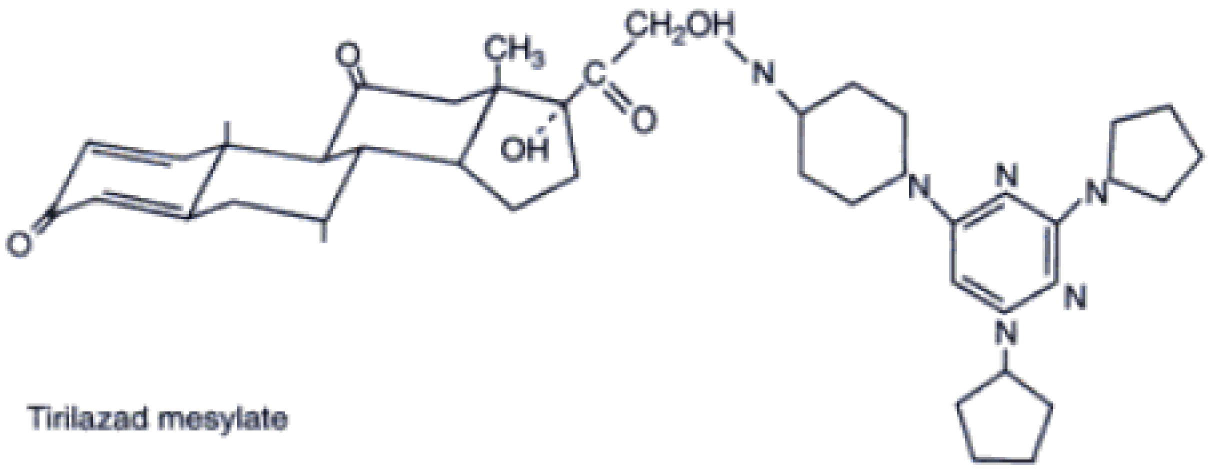
In a feline model of spinal injury, methylprednisolone (30 mg/kg) attenuates post-traumatic lipid peroxidation. In addition, and perhaps because of the inhibitory effect on lipid peroxidation, methylprednisolone also supports energy metabolism, reduces or prevents post-traumatic ischemia and neurofilament degradation, reduces intracellular calcium accumulation (resulting in the AA cascade), and inhibits vasoactive prostaglandins ($PGF_{2\alpha}$ and thromboxane). In addition, like other steroids, methylprednisolone may increase spinal neuronal excitability, which may also be important to neurophysiologic recovery. Several pertinent points must be appreciated regarding these effects of methylprednisolone on spinal cord injury. First, these effects occur only at a high concentration (i.e., that achieved with an IV dose of 30 mg/kg). Second, the effects are biphasic, with loss at 60 mg/kg. As with many protective mechanisms, the drug must be administered early in the pathophysiologic process because spinal uptake of methylprednisolone decreases rapidly with time after injury. Loss of effect may reflect a decrease in blood flow to damaged tissues or the irreversible nature of lipid peroxidase. Finally, the time course of neuroprotection of methylprednisolone follows the disappearance of the drug from plasma or tissue—that is, it lasts only 2 to 6 hours (the half-life of the drug in feline spinal tissue). Thus, the drug must be administered frequently to preserve tissues and maximize the potential for recovery.

Lazaroids

After the unique protective effect of methylprednisolone among the glucocorticoids in damaged nerve tissue was recognized, attempts were made to refine the structure of the steroidal molecule such that the neuroprotective (antilipid peroxidase) effects would be maintained but the glucocorticoid effects minimized. The result of these efforts was the synthesis of the 21-aminosteroids or lazaroids. Tirilazad mesylate is the prototypic drug (Fig. 16–11). These drugs have been specifically designed to localize in cell membranes and inhibit (iron-mediated) lipid peroxidase. Although initial investigations were oriented toward acute trauma, because inhibition of lipid peroxidase may decrease neuronal degeneration, these drugs may also be useful for chronic neurodegenerative processes.

Tirilazad mesylate is a very lipophilic drug that preferentially distributes to the lipid components of cell membranes. Because neuronal tissue is composed of a greater proportion of lipid components, these drugs preferentially accumulate in neuronal tissue. Its pharmacologic actions are complex and include a radical scavenging/antioxidant effect and a physiochemical interaction with the cell membrane such that the fluidity of the membrane is decreased (Fig. 16–12). Although action against iron-mediated lipid peroxidase was sought for these drugs, they will in fact

Figure 16–11. Tirilazad mesylate is an example of a lazaroid (a 21-aminosteroid).



Tirilazad mesylate

inhibit lipid peroxidase in iron-free systems as well. Tirilazad has proved to be an effective inhibitor of lipid peroxidase in all in vitro models studied. It also acts to reduce hydroxyl radicals either by direct scavenging abilities or decreased lipid peroxidase. Stabilization of cell membranes is considered an important part of its protective action. The nitrogen component of the steroid is thought to interact with the phosphate of the "head" groups (hydrophilic portion) of the bilipid layer via ionic interactions. The steroidal component localizes in the lipophilic portion of the membrane, compressing the phospholipid groups. Restriction of the movement of the cell membrane reduces the potential for lipid peroxidase by restricting the movement of lipid peroxyl and alkoxyl radicals in the membrane.

Tirilazad also has a high affinity for vascular endotheliulm. It appears to be able to protect vascular endothelium from damage by reactive oxygen species, possibly by preserving endothelium-derived relaxing function. It also appears to protect the blood-brain barrier against traumatically or chemically induced permeability. Tirilazad may protect other endothelial cells during trauma or hypoxic damage such as the hepatic endothelium during hemorrhagic shock.

Animal models used to study the effects (not safety) of tirilazad have been primarily rats and monkeys. A few studies have focused on dogs or cats. Models of CNS damage have included that induced by cardiac arrest, altered cerebral blood flow, and subarachnoid hemorrhage. The clinical pharmacology of tirilazad has been studied in humans. It appears to be a flow-limited hepatically cleared drug. In humans, there is a discrepancy in the elimination half-life that approximates 4 hours in one report and, after steady state, approximates 35 hours. The difference appears to be a longer terminal phase after multiple dosing compared with single dosing; it is likely that volume of distribution cannot be accurately assessed after single dosing. The disposition of tirilazad is linear and does not appear to change with plasma drug concentration. Safety studies in humans have revealed the drug to be safe. Pain occurs at the site of injection, but this has been overcome by dilution of the drug, a change in the site of injection, and frequent catheter changes. Tirilazad does not appear to adversely affect the heart, blood pressure, or hepatic or renal function. Tirilazad has no glucocorticoid activity and will not alter parameters indicative of glucocorticoids (i.e., glucose, hematologic indices, adrenocorticotropic hormone, or cortisol). Apparent indications for tirilazad in people include acute head or spinal injury, subarachnoid hemorrhage, and ischemic stroke.

The lazaroids have also demonstrated efficacy in traumatic shock (Aoki and Lefer, 1990), hemorrhagic shock (Hall et al., 1988), and endotoxemia (Semrad et al., 1989, 1993). Lazaroids decrease neutrophil accumulation, maintain arterial pressure, decrease myocardial injury, and increase survival. Lazaroids decrease formation of the eicosanoid mediators and production of TNF. When administered to dogs within 30 minutes of endotoxin infusion, lazaroids attenuated the effects of endotoxin (Zhang et al., 1995). Further studies are indicated before the use of lazaroids is confirmed. Currently, no lazaroid is approved for use in the United States.

Figure 16–12. Devoid of glucocorticoid activity, the 21-aminosteroids are thought to provide a neuroprotective effect in part by insertion into the lipid bilayer of the cell membrane. Cell membrane fluidity is decreased, thus impairing the ability of oxygen radical formation to cascade across the lipid layer. Lipid peroxidation is thus minimized.

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17

Glucocorticoid Therapy in the Dog and Cat

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Katrina A. Mealey

INTRODUCTION
PHYSIOLOGY: CONTROL OF ENDOGENOUS GLUCOCORTICOID SECRETION
MECHANISM OF ACTION
PHYSIOLOGIC EFFECTS
Effects on Intermediary Metabolism: Carbohydrates, Proteins, and Lipids
Water and Electrolyte Balance
Hemolymphatic System
Anti-inflammatory and Immunosuppressive Effects
Cardiovascular System
Bone and Cartilage
Skeletal Muscle
Central Nervous System
Respiratory System
Alimentary Tract
Reproduction
STRUCTURE-ACTIVITY RELATIONSHIP
CLINICAL PHARMACOLOGY
Absorption
Distribution, Metabolism, and Excretion
PREPARATIONS
Hydrocortisone
Prednisolone and Prednisone
Methylprednisolone
Dexamethasone
Betamethasone
Beclomethasone
Tirilazad Mesylate
Fludrocortisone
Desoxycorticosterone Pivalate
THERAPEUTICS
THERAPEUTIC INDICATIONS
Dermatologic
Otic
Respiratory
Musculoskeletal
Central Nervous System
Inflammatory Bowel and Liver Disease
Gingivitis and Stomatitis
Shock
  Septic Shock
  Hemorrhagic Shock
Neoplasia
Ophthalmologic
Hematopoietic
Hypoadrenocorticism
ADVERSE EFFECTS
Central Nervous System
Musculoskeletal
Gastrointestinal and Liver
Metabolic
Endocrine
Renal
Cardiovascular
Immune Function
Respiratory
Growth Retardation
CONTRAINDICATIONS
Infectious Disease
Diabetes Mellitus
Renal Failure
Corneal Ulceration
Pancreatitis
Gastrointestinal Ulceration
Pregnancy
Epilepsy

INTRODUCTION

Glucocorticoids are among the most frequently used and misused drugs in veterinary medicine. Optimal therapy with glucocorticoids requires a thorough understanding of their actions on all body systems and knowledge of the pharmacodynamic and pharmacokinetic differences of the synthetic glucocorticoid derivatives. The physiologic and pharmacologic effects of glucocorticoids have not been extensively studied in the dog or cat; therefore much of the information presented represents data extrapolated from human patients or rodent studies. Where possible, information specific to the dog or cat has been included and indicated as such.

PHYSIOLOGY: CONTROL OF ENDOGENOUS GLUCOCORTICOID SECRETION

Corticotropin-releasing factor (CRF) is secreted by the hypothalamus and travels through the hypophyseal portal system to the adenohypophysis where it stimulates the synthesis and secretion of adrenocorticotropin (ACTH) from the basophilic cells of the adenohypophysis (Fig. 17–1). In addition to its role in promoting ACTH secretion, CRF appears to be involved in the autonomic, immunologic, and behavioral response to stress independent of the hypothalamopituitary axis. Administration of CRF to dogs results in a decrease in gastric acid secretion by activation of the sympathetic nervous system, an immediate decrease in mean arterial blood pressure accompanied by reflex tachycardia, and a marked increase in plasma vasopressin concentrations (Mol et al., 1994). These actions of CRF are independent of glucocorticoids.

The primary function of ACTH is to stimulate the adrenal cortex to synthesize and secrete cortisol, corticosterone, aldosterone (the effect of ACTH on mineralocorticoid secretion is minimal), and weak androgenic substances. Cortisol and corticosterone concentrations in plasma influence CRF and ACTH secretion such that increased concentrations inhibit release of CRF and ACTH, and reduced concentrations stimulate release of CRF and ACTH. Exogenous factors, such as trauma, heat, stress, and surgery, and neural impulses also mediate CRF and ACTH secretion. Exogenous corticosteroid administration can also suppress CRF and ACTH release. The degree of suppression de-

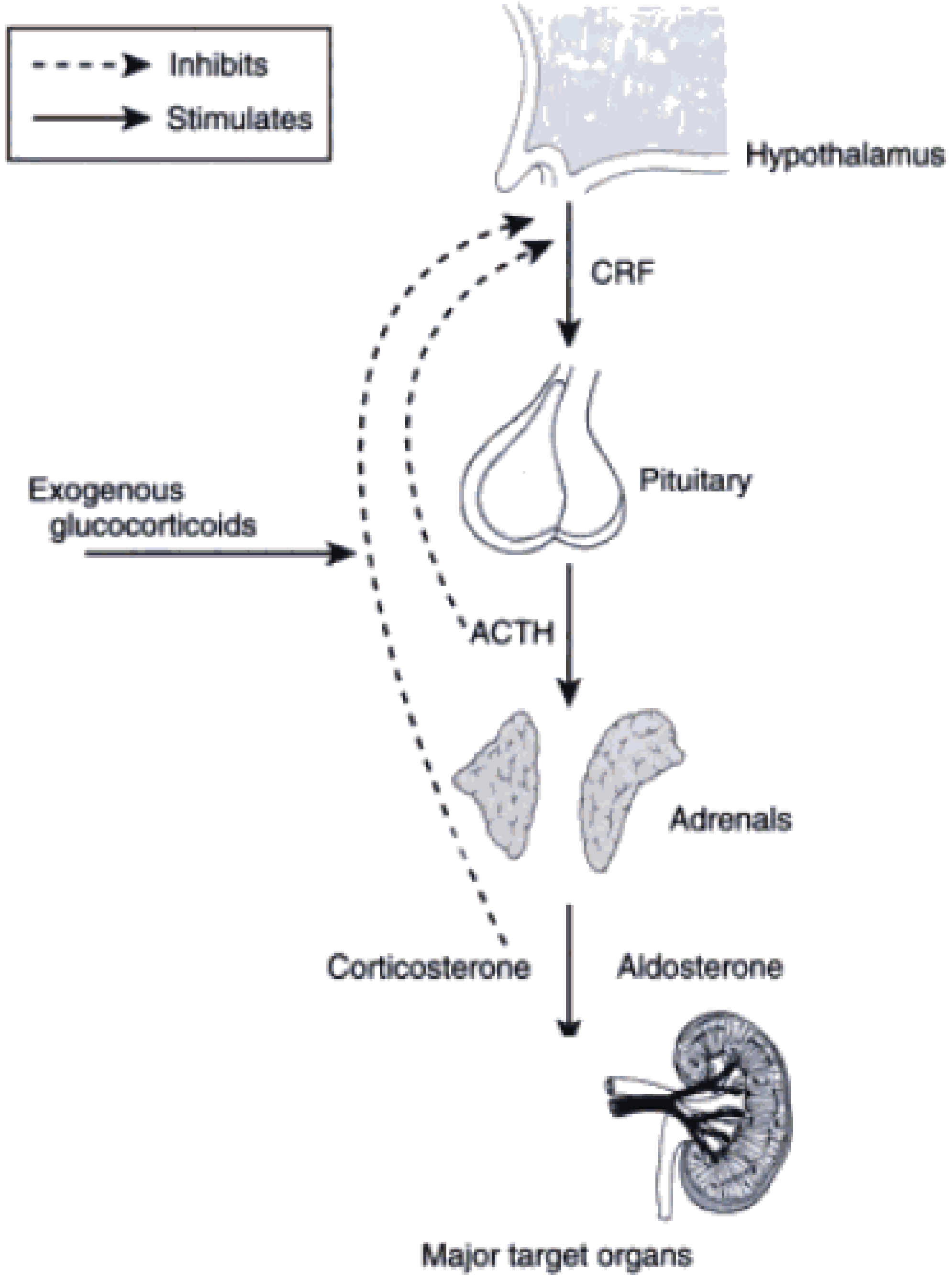

Figure 17–1. The relationship between the hypothalamus, pituitary, and adrenal glands. Release of corticotropin-releasing factor (CRF) is prevented by feedback inhibition of corticosteroids (exogenous or endogenous). Release of adrenocorticotropic hormone (ACTH) is subsequently inhibited, and further synthesis, primarily of glucocorticoids, is inhibited. The primary target organ of mineralocorticoids is the kidney; the liver and cardiovascular system are important targets of glucocorticoids.

pends on the particular drug used. For example, dexamethasone is 50 to 100 times more potent in suppressing ACTH secretion than is cortisol (Feldman and Nelson, 1987a). The diurnal variation in glucocorticoid secretion that occurs in humans has not been well documented in dogs or cats.

MECHANISM OF ACTION

The myriad of physiologic effects of glucocorticoids result from interaction of the drugs with glucocorticoid receptors. Selected activities may, however, be mediated through nonreceptor mechanisms. At least three glucocorticoid receptors have been identified, each associated with different physiologic effects (Funder, 1992). Differences in alpha- and beta-glucocorticoid receptors in RNA ratios and concentrations differ among tissues, suggesting differential gene regulation by glucocorticoids in different cells (Korn, 1998). Although every cell type appears to have glucocorticoid receptors, the liver is the primary target. The type and concentration of receptor varies between species and tissue. Within a given tissue, receptor numbers may fluctuate with changing cell cycles and age and in response to a variety of endogenous or exogenous compounds. Over 15 endogenous regulators have been identified for glucocorticoid receptors (Burnstein and Cidlowski, 1992).

Glucocorticoid receptors are located in the cytoplasm of the target cell associated with heat shock proteins and an immunophilin, an intracellular protein that binds other immunosuppressive compounds (Schimmer and Parker, 1995). The receptor is inactivated until bound to a steroid ligand (Schimmer and Parker, 1995). Steroids enter the cells by passive diffusion, although a rate-limited active transport mechanism may also exist. Once in the cell, the glucocorticoid binds to the receptor, the heat shock protein and other molecules dissociate, and the resulting activated receptor-glucocorticoid complex translocates to the nucleus (Fig. 17–2). In the nucleus, the complex binds to regulatory proteins of target genes. The short DNA sequences recognized by the activated glucocorticoid receptor are referred to as *glucocorticoid responsive elements.* It is through these glucocorticoid responsive elements that specificity of glucocorticoid-modulated gene transcription is controlled. Transcription of the gene and subsequent formation of the targeted protein is either induced or inhibited. Some of the proteins that are regulated by glucocorticoids are listed in Table 17–1. The proteins encoded by these genes are responsible for the physiologic (pharmacologic) effects of glucocorticoids. The receptor and glucocorticoid are eventually metabolized (the exact location or timing is not documented). The cellular half-life of the activated complex is about 10 hours (Bodine and Litwack, 1990). It is not known if the rate of metabolism of the glucocorticoid-receptor complex is dependent on the specific glucocorticoid involved.

In general, the mineralocorticoid receptor acts similarly to the glucocorticoid receptor and may be identical in structure (Schimmer and Parker, 1995). No differences have been described for glucocorticoid and mineralocorticoid DNA recognition motifs. Differences in action between these two steroids reflect in part different abilities to activate discrete sets of target genes. This may reflect a difference in repression of transcriptional induction. In addition, mineralocorticoid receptors have restricted expression, with the principle sites including the cortical distal tubules and collecting ducts, the colon, salivary and sweat glands, and the hippocampus. Differences in steroidal action also are independent of receptor interaction. Metabolism of the different steroids (e.g., aldosterone vs. cortisol) by enzymes (e.g., 11β-hydroxysteroid dehydrogenase) located in steroid-responsive tissues (e.g., kidney, colon, salivary glands) appears to provide an enzymatic barrier by inactivating the steroid (e.g., cortisol) to which the tissue should not preferentially respond. Certain disease conditions may actually reflect an absence of the metaboliz-

Table 17–1. Examples of Proteins Whose Synthesis Is Targeted by Glucocorticoid Receptor Regulation

Induced	Inhibited
Lipocortin-1	Cytokines
β_2-Adrenoreceptor	Natural killer$_1$ receptor
Angiotensin-converting enzyme	Inducible nitric oxide synthase
Neutral endopetidase	Cyclooxygenase$_2$
β_2-Adrenoreceptor	Endothelin$_1$
Na^+, K^+-ATPase (mineralocorticoid)	Phospholipase$_2$
	Collagenase
	Stromelysin

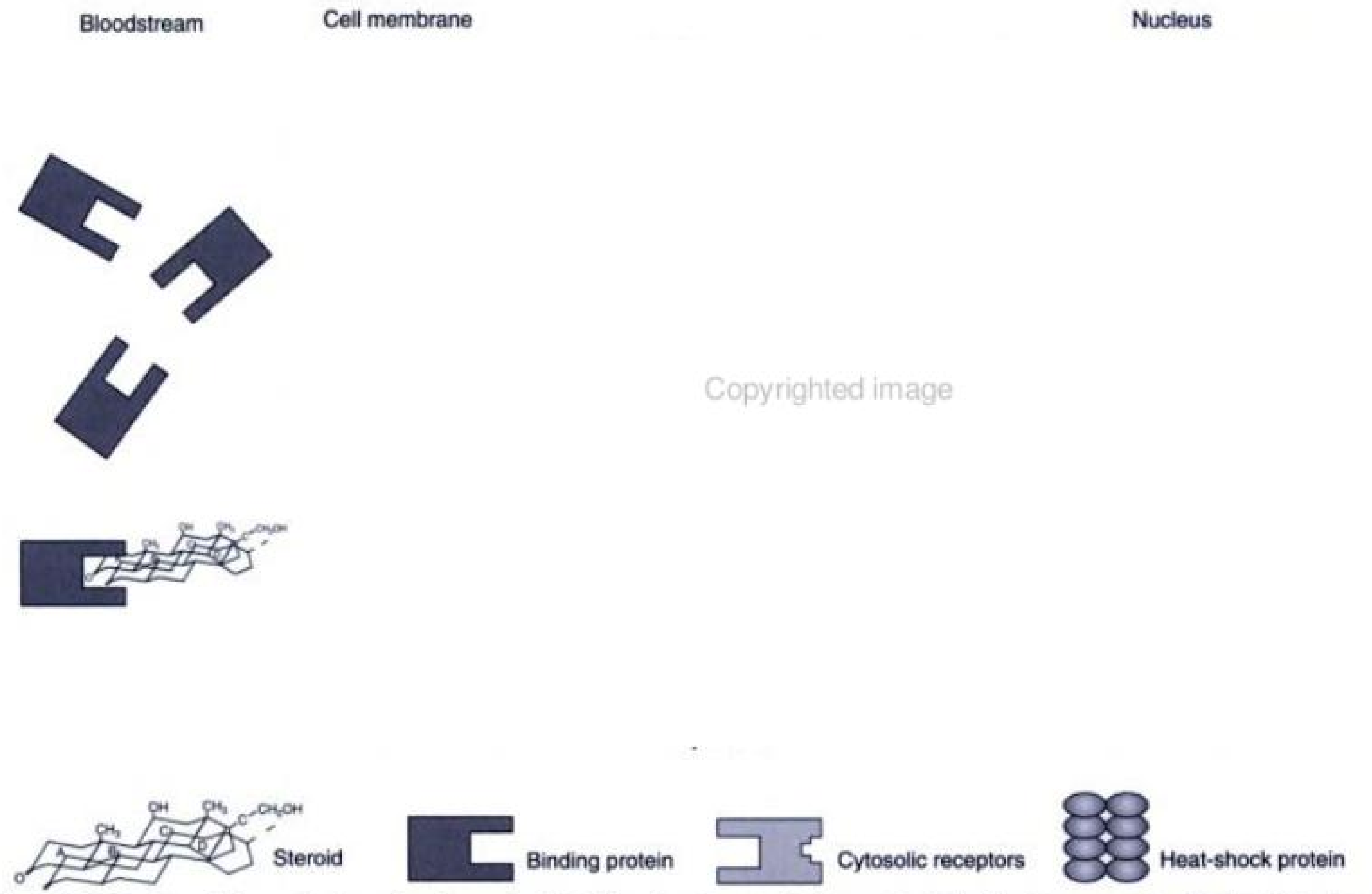

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Figure 17–2. The intracellular mechanisms of a glucocorticoid include release from its binding protein in the bloodstream, passive diffusion of the drug through the cell membrane, interaction with the cytoplasmic receptor (associated with a heat-shock protein), translocation to the nucleus, binding to DNA, transcription and protein synthesis, and degradation of the protein-steroid complex.

ing enzyme, allowing the tissue to respond inappropriately to the inappropriate steroid (Schimmer and Parker, 1995). Aldosterone activates the expression of several genes, with that of Na^+,K^+-ATPase in the basolateral membranes of tubular cells being the most characterized.

Interestingly, cortisone can have different and opposing effects, depending on whether it interacts with mineralocorticoid or glucocorticoid receptors. Cortisone inhibits microglial proliferation through glucocorticoid receptors but stimulates proliferation through mineralocorticoid receptors (Tanaka et al., 1997). Dexamethasone also inhibits microglial cell proliferation at concentrations lower than cortisone (Tanaka et al., 1997).

Failure to respond to steroid therapy is observed in human patients being treated for a variety of diseases. The documented phenomenon of glucocorticoid resistance (both familial and iatrogenic forms have been reported in humans) may reflect, among other causes, reduced receptor numbers or affinity for glucocorticoid (Lamberts et al., 1992). Cellular response to glucocorticoids has been directly correlated with receptor numbers. Reversible down-regulation of receptor numbers and a subsequent decrease in biologic effect is a documented sequela of glucocorticoid treatment (Burnstein and Cidlowski, 1992).

PHYSIOLOGIC EFFECTS

Physiologic effects of glucocorticoids are those actions required for the "normal" day-to-day function of the animal. These effects can be easily appreciated when glucocorticoids are absent, as in the case of adrenocortical insufficiency (hypoadrenocorticism or Addison disease), or present in excessive concentrations, as in hyperadrenocorticism.

Effects on Intermediary Metabolism: Carbohydrates, Proteins, and Lipids

The natural function of glucocorticoids is to protect glucose-dependent cerebral functions by stimulating the formation of glucose by the liver, decreasing its peripheral utilization and promoting its storage as glycogen (Haynes, 1990). Teleologically, these effects protect glucose-dependent tissues, the brain and heart, from starvation (Schimmer and Parker, 1995). The hyperglycemic effect of glucocorticoids, as seen in the stressed patient, is due to an increase in gluconeogenesis and insulin antagonism. Gluconeogenesis is the result of an increase in precursors necessary for gluconeogenesis as well as induction of hepatic enzymes that catalyze reactions of glucose synthesis. Increased breakdown of proteins, particularly skeletal muscle and collagen, provides gluconeogenic precursors (e.g., amino acids and glycerol). This effect is exhibited clinically as muscle wasting, delayed wound healing, and thinning of the skin. The anti-insulin effect of glucocorticoids is a result of decreased peripheral tissue utilization of glucose and reduced affinity of cellular receptors for insulin. Utilization appears to be decreased by translocation of insulin receptors from the cell membrane to an intracellular location inaccessible by insulin (Schimmer and Parker, 1995).

Metabolism of lipids is also affected by glucocorticoids. Specifically, glucocorticoids promote lipolysis, generating the free fatty acids that, along with amino acids, serve as substrates for hepatic glycogen synthesis and inhibit long-chain fatty acid synthesis. Effects of glucocorticoids on lipid metabolism reflect, in part, a permissive effect of the steroids on other agents, including growth hormone and β-adrenergic receptors. One sequela of these effects is redistribution of body fat (such as is typified by Cushing disease). Differences in adipocyte sensitivity to insulin and the facilitating effects of glucocorticoids may explain the redistribution phenomenon (Schimmer and Parker, 1995).

Water and Electrolyte Balance

Aldosterone is the most potent, natural corticosteroid that impacts fluid and electrolyte balance. Mineralocorticoids act to enhance sodium reabsorption in exchange for potassium (from the distal renal tubules and collecting ducts) or hydrogen (the itercalated cells), resulting in a positive sodium balance, expansion of extracellular fluid volume, and an increase in glomerular filtration rate. Sodium reabsorption is enhanced by increasing the number of open Na^+ and K^+ pores; Na^+,K^+-ATPase activity at the basolateral membrane also is increased, causing sodium to be returned to the circulation. The ratio of monocationic molecules exchanged is not limited to 1:1.

Effects of mineralocorticoids are not limited to renal tissues but also include the colon, ilium, ciliary apparatus, and salivary and (in human beings) sweat glands. Glucocorticoids influence water and electrolyte balance through mineralocorticoid actions. Differences in tissue to response to various corticosteroids was addressed previously. Cortisol and the synthetic glucocorticoids possess varying degrees of mineralocorticoid activity, but all have less than 1% of the mineralocorticoid activity of aldosterone. Glucocorticoids also impart a permissive effect on tubular mechanisms that maintain the glomerular filtration rate. Glucocorticoids have an inhibitory effect on antidiuretic hormone and may decrease permeability of the distal renal tubules to water via a direct action. The polyuria/polydipsia commonly observed in dogs (but not cats) receiving glucorticoids may be a result of a combination of mineralocorticoid and glucocorticoid effects.

Glucocorticoids influence several aspects of calcium movement. In the renal tubular cells, calcium excretion is increased, and in the small intestine its absorption is impaired. Glucocorticoids also increase parathormone secretion, which in turn increases osteoclast-mediated bone resorption. The net effect of glucocorticoids on calcium homeostasis is a decrease in total body calcium stores.

Hemolymphatic System

Glucocorticoids tend to increase the red blood cell content of the blood by retarding erythrophagocytosis. Lymphopenia, eosinopenia, and monocytopenia due to cellular redistribution and neutrophilia due to increased release from bone marrow, demargination, and a reduction of their removal from the circulation are all associated with glucocorticoid administration (Schimmer and Parker, 1995). This blood cell profile represents the "stress leukogram" seen clinically in patients with elevated concentrations of endogenous glucocorticoids. The acute effects of glucocorticoids on circulating lymphocytes are due to sequestration from the blood rather than lymphocytolysis, although cells of lymphocytic malignancies are destroyed by glucocorticoids. In addition to reducing the number of circulating lymphocytes, glucocorticoids also alter the responses of lymphocytes to mitogens and antigens. T lymphocytes are inhibited to a greater degree than B lymphocytes (see following discussion of immunomodulation).

Anti-inflammatory and Immunosuppressive Effects

Glucocorticoids are most frequently used in clinical medicine for their anti-inflammatory and immunosuppressive actions (Table 17–2). Because the anti-inflammatory and immunosuppressive effects of glucocorticoids reflect specific actions on white blood cells, these effects are inextricably linked. They generally occur only when the amounts of steroid are present in concentrations greater than those found in the normal physiologic state (i.e., pharmacologic concentrations). The effects of glucocorticoids on leukocyte numbers was discussed earlier. Glucocorticoids also profoundly affect white blood cell function. Ultimately, both the humoral and cell-mediated arms of the immune response are impacted.

Glucocorticoids inhibit early and late phases of the inflammation. Responses that are inhibited include edema formation, fibrin deposition, leukocyte migration, phagocytic activity, collagen deposition, and capillary and fibroblast proliferation. Many of these processes involve lymphokines and other soluble mediators of inflammation, and it is through these mediators that glucocorticoids exert their anti-inflammatory actions. Specifically, glucocorticoids inhibit (via lipocortin) the enzyme phospholipase A_2, which converts arachidonic acid to prostaglandin and leukotriene metabolites (Fig. 17–3). Glucocorticoids also may specifically, yet preferentially, inhibit cyclooxygenase 2, the inducible form of cyclooxygenase (Ristimaki et al., 1996; Crofford et al., 1994). The net effect of this specificity may be inhibition of inflammatory prostaglandins without negatively impacting the protective effects of prostaglandins in other body systems (e.g., gastrointestinal, renal, hemostasis).

Glucocorticoids also inhibit release of tumor necrosis factor and interleukin-2 (IL-2) from activated macrophages. Tumor necrosis factor induces cytotoxicity and can enhance neutrophil and eosinophil function (Haynes, 1990). The effects of IL-2 are mainly involved in immune function and are discussed later. The release of platelet-activating factor from leukocytes and mast cells is inhibited by glucocorticoids. Platelet-activating factor induces vasodilation, platelet and leukocyte aggregation, smooth muscle contraction (especially in the bronchi), and increased vascular permeability (Campbell, 1990). The action of macrophage

Table 17–2. Guidelines for Corticosteroid Usage

Steroid Name	Trade Name	Relative Anti-inflammatory Strength	Forms Available	Dose (Dogs/Cats)	Duration	Comments
Hydrocortisone	Cortef Hydrocortone	1	Tablets, 5, 10, 20 mg	0.5–2.25 mg/lb PO q12h 2.25 mg/lb IM/IV q24h	<12 h	Not for alternate-day use or long-term anti-inflammatory therapy; used in many topicals
Hydrocortisone sodium succinate	Solu-Cortef A-Hydrocort		100, 250, 500, 100 mg vials	10–30 mg/lb IV q3–6h		
Cortisone acetate		0.8		Dogs: 1 mg/lb IM q24h; 0.25–0.33 mg/lb PO q6–8h	<12 h	Rapid onset, but short acting and low potency; activity takes place only after conversion to hydrocortisone
Prednisone, prednisolone	Prednisone: Deltasone, Meticorten, Orasone Prednisolone: Delta-Cortef, Prelone	4	Prednisone: 1, 2.5, 5, 10, 20, 25, 50 mg tablets; 10 mg/mL (100 mL vial), 40 mg/mL (50 mL vial) Prednisolone: 5 mg tablets; 20 mg/mL (50 mL vial), syrup 5 mg/15 mL	0.25–0.5 mg/lb PO/IM/IV/SC q12h initially, then taper to lowest dose q48h. *In general:* Anti-Itch: 0.25 mg/lb Anti-inflammatory: 0.5 mg/lb Immunosuppressant: 1–2 mg/lb (SID × 4–6 wks)	12–36 h	Good for alternate-day use. Prednisolone works alone; prednisone must be converted to prednisolone by the liver (so use prednisolone if liver disease present). Anti-itch and anti-inflammatory dose = 4–7 doses SID then taper to 4–7 doses SID every other day
Prednisolone sodium succinate	Delta-Cortef	7	100, 500 mg/vial (single-use vials containing 10 mL diluent)	2.5–10 mg/lb IV, repeat as needed for shock at 1, 3, 6, and 10 h 0.25–0.5 mg/lb q12–24h	<12 h	Do not use 50 mg/mL formulation for IM injection (too irritating)
Prednisolone sodium phosphate	Cortisate		20 mg/mL (50 mL vials)	5–15 mg/lb IV q2–3h as needed		Must be used early in shock and in massive doses
Methylprednisolone	Medrol	5	Tablets, 1, 2, 4, 8, 16, 24, 32 mg	0.03–0.5 mg/lb PO q8h	12–36 h	OK for alternate-day use
Methylprednisolone acetate	Depo-Medrol	5	20 mg/mL (10, 20 mL vials); 40 mg/mL (5 mL vials)	Dog: 0.5–1 mg/lb IM/SQ, may repeat in 4 weeks Cat: 1–2.5 mg/lb q14 days Intralesional: 10–40 mg, 10–20 mg per joint IA	Injectable form is in insoluble solution with 4–6 weeks duration of activity	Long acting and potent, so use with caution; about same potency and duration as triamcinolone (see triamcinolone comments)
Methylprednisolone sodium succinate	Solu-Medrol A-Methapred		40, 125, 500, 1000, 2000 mg/vial	7.5–15 mg/lb IV q2–3h	<24 h	Best choice for CNS trauma and reperfusion injuries because good O_2 radical scavenger
Triamcinolone acetonide	Vetalog	5	Tablets, 0.5, 1.5 mg; powder, 15 mg/packet; 2 mg/mL, 6 mg/mL	0.05–0.1 mg/lb PO/IM/SC Dog: 5 mg per joint IA Cat: 1–3 mg per joint IA Intralesional: 1–2 mg per lesion (max 6 mg)	12–36 h (oral); injectable form is in insoluble solution with 4–6 weeks duration of activity	Not for alternate-day use due to suppression of HPA axis
Dexamethasone	Azium	30	Tablets, 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6 mg; powder 10 mg/packet	0.025–0.075 mg/lb PO/IV/IM/SC q24h *In general:* Anti-itch: 0.025 mg/lb Anti-inflammatory: 0.05 mg/lb Immunosuppressant: 0.1 mg/lb	48–72 h	Not for alternate-day use because long acting; propylene glycol vehicle (injectable form) can cause arrhythmias and sudden death if give IV rapidly
Dexamethasone sodium phosphate	Azium SP	30	4, 10, 20, 24 mg/mL	1–3 mg/lb IV, followed in 6–8 h by 0.25–0.5 mg/lb IM/SC q8–12h	<2 h	Activity occurs within minutes (gets in cells faster than Azium); used in life-threatening situations
Betamethasone	Betasone	30	5 mg/mL (diproprionate) and 2 mg/mL (sodium phosphate) in 5 mL vials	0.25–0.5 mL/20 lbs IM, not more than two treatments	48–72 h; insoluble ester provides 4–5 weeks duration of action	Potent, long acting, not for alternate-day use
Flumethasone	Flucort	30	Tablets, 0.0625 mg, 0.5 mg/mL in 100 mL vials	0.03–0.125 mg/lb PO/IV/IM/SC q24h	32–48 h	Potent, long acting

Abbreviations: CNS = central nervous system; HPA = hypothalamic-pituitary-adrenal axis; IA = intra-articular; IM = intramuscular; IV = intravenous; PO = oral; SC = subcutaneous; SID = once a day.

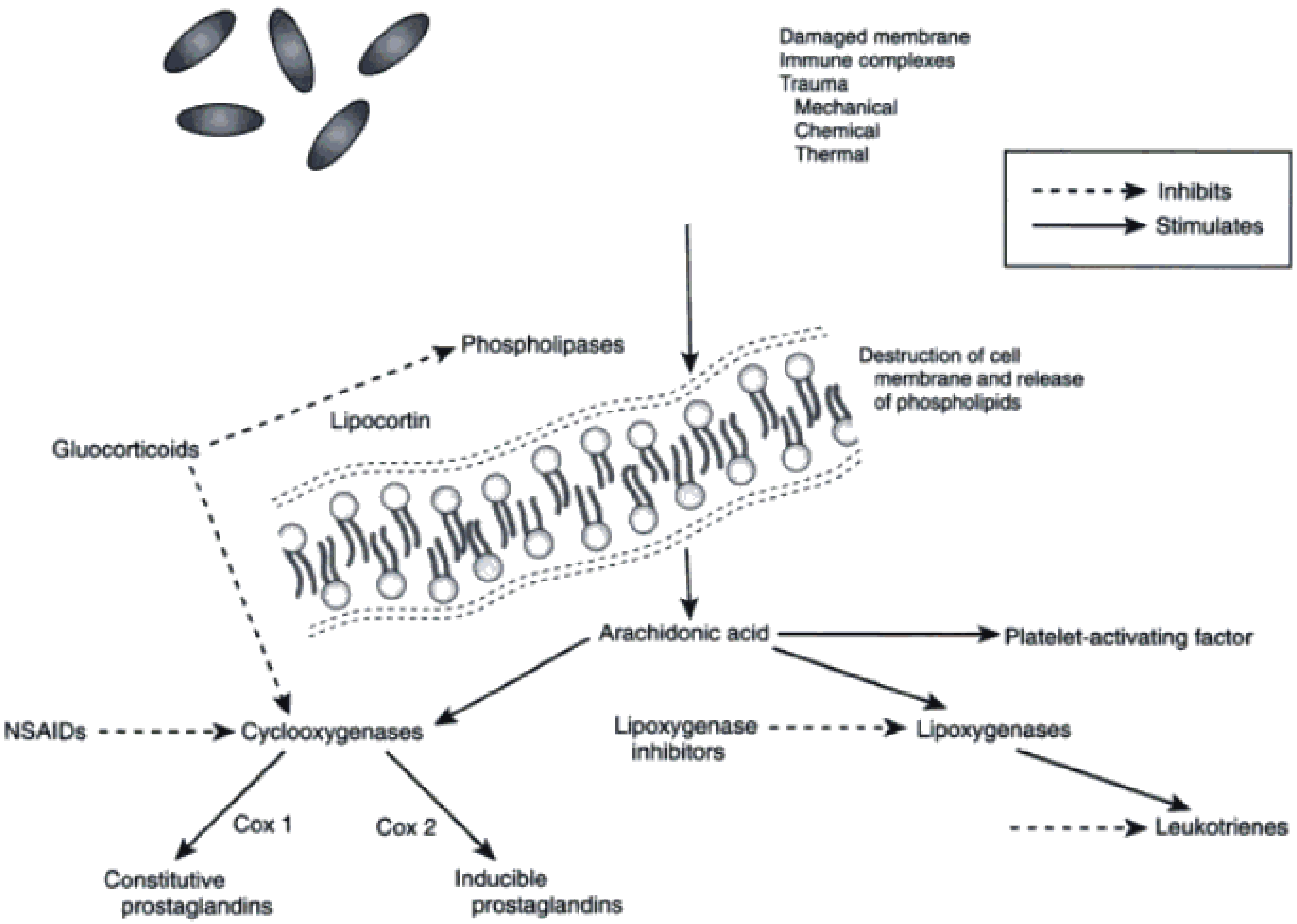


Figure 17–3. Site of glucocorticoid action in the inflammatory response. Glucocorticoids act primarily to inhibit phospholipase and its subsequent degradation of cell membrane phospholipids to mediators of inflammation (leukotrienes and prostaglandins). Lipocortin is the effector protein whose synthesis is stimulated by glucocorticoids. NSAIDs = nonsteroidal anti-inflammatory drugs. Glucocorticoids selectively inhibit cyclo-oxygenase 2.

migration-inhibition factor, namely, to arrest the movement of macrophages at antigenic sites, is inhibited by glucocorticoids. Consequently, macrophages migrate away from the affected area. Glucocorticoids also alter synthesis of and biologic response to collagenase, lipase, and plasminogen activator. The anti-inflammatory effects of glucocorticoids also may reflect inhibition of the inducible form of nitric oxide synthase (iNOS) (Yang, 1998). Synovial macrophage nitric oxide production and iNOS synthesis are inhibited by dexamethasone. The inhibitory effect appears to be mediated by lipocortin.

The immunosuppressive actions of glucocorticoids are more pronounced on the cellular arm than the humoral arm of the immune system (Fig. 17–4). Glucocorticoids have minimal effects on plasma immunoglobulin concentrations but can modulate immunoglobulin function. For example, opsonization of bacteria is inhibited. Therapeutic doses of glucocorticoids do not significantly decrease an animal's antibody response to antigenic challenge (e.g., vaccinations). The immunosuppressive actions of glucocorticoids, like their anti-inflammatory actions, involve disruption of intercellular communication of leukocytes via interference with lymphokine production, biologic action, or both. Glucocorticoids block the effects of the migration-inhibition factor-γ and interferon-γ (IFN-γ) on macrophages (Haynes, 1990). IFN-γ, which is released from activated T cells, plays an important role in facilitating antigen processing by macrophages.

Glucocorticoids inhibit the synthesis and release of IL-1 by macrophages, thereby suppressing the activation of T cells. Glucocorticoids also inhibit IL-2 synthesis by activated T cells. Interleukin-2 plays a critical role in amplification of cell-mediated immunity. Additionally, glucocorticoids suppress the bactericidal and fungicidal actions of macrophages.

The immunsuppressive effects of glucocorticoids may also reflect actions on the hypothalamic-pituitary-adrenal axis. Multiple cytokines appear to regulate this axis. Specifically, IL-1 appears to stimulate the release of CRH, directly increase the release of ACTH, and may cause the adrenals to release glucocorticoids. These interactions appear to be important to modulation of stress and thus maintenance of homeostasis (Schimmer and Parker, 1995).

Cardiovascular System

Corticosteroids have two major effects on the cardiovascular system. Mineralocorticoids and, to a lesser extent, glucocorticoids impact the maintenance of extracellular fluid volume as described previously. Interestingly, mineralocorticoids also appear to have direct actions on cardiovascular tissues; increased cardiac fibrosis has been induced experimentally in rats by administration of excessive mineralocorticoids, suggesting an indication for spironolactone as a diuretic in congestive heart failure associated with myocardial disease. (Schimmer and Parker, 1995). In addition, corticosteroids (predominantly glucocorticoids) enhance vascular reactivity to other vasoactive substances (e.g.,

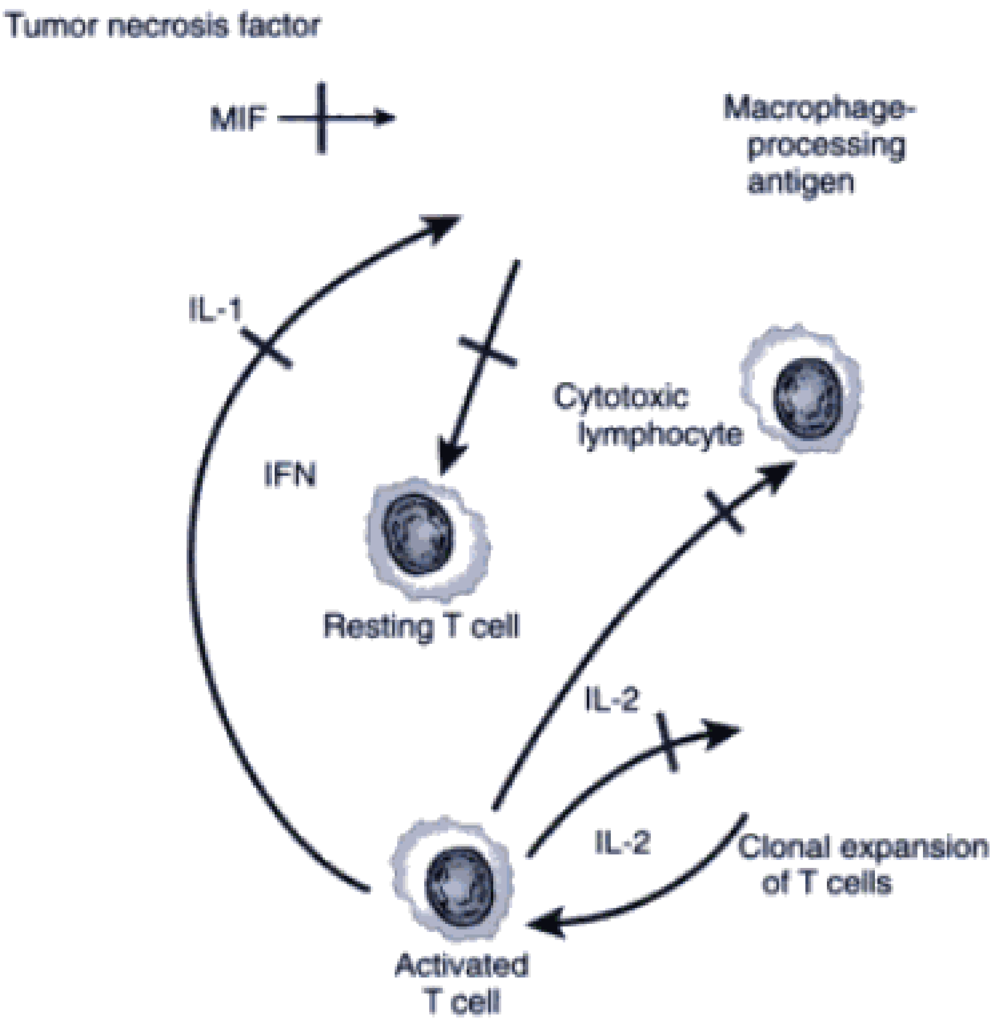


Figure 17–4. Glucocorticoids exert inhibitory effects at several sites in the cell-mediated response. Both macrophages and T cells are targeted. IFN = interferon; IL = interleukin; MIF = migration-inhibition factor.

norepinephrine, angiotensin II) (Schimmer and Parker, 1995).

Mechanisms appear to include increased receptor numbers in the vascular wall or other tissues. Other proposed mechanisms of glucocorticoid-induced hypertension include reduced activity of depressor systems (e.g., kallikrein-kinin, prostaglandins, and nitric oxide) and increased responsiveness to angiotensin II and norepinephrine (Saruta, 1996). In human patients with hyperadrencorticism, hypertension occurs. In contrast, in patients with insufficient concentrations of glucocorticoids, negative sequelae include increased capillary permeability, decreased cardiac output, and inadequate vasomotor response of the smaller blood vessels to catecholamines.

Bone and Cartilage

Glucocorticoids antagonize the effects of vitamin D_3, accelerate bone resorption, and decrease bone formation (via direct action on osteoblasts), resulting in osteoporosis. This phenomenon is well documented in humans patients after chronic glucocorticoid therapy, but to the authors' knowledge it has not been observed in animals (Seale and Compton, 1989). At supraphysiologic doses, glucocorticoids inhibit collagen synthesis by fibroblasts, depress chondrocyte metabolism, and decrease the proteoglycan content of cartilage, resulting in morphologic changes in articular cartilage (Glade et al., 1983; Adams, 1992).

Skeletal Muscle

The permissive effects of glucocorticoids include their influence on the ability of skeletal muscle to function normally. Too little will result in muscle wasting (generally due to hypokalemia). Likewise, and paradoxically, too much also will result in muscle wasting. Increased use of amino acids from muscle proteins is likely to contribute to this effect. Although the exact mechanisms of muscle wasting are unknown, the term *steroid myopathy* has been coined to reflect this condition in human patients and is used to refer to similar manifestations in small animals with hyperadrenocorticism (Schimmer and Parker, 1995).

Central Nervous System

Indirectly, glucocorticoids maintain adequate plasma concentrations of glucose for cerebral functions, maintain cerebral blood flow, and influence electrolyte balance in the central nervous system (CNS). Glucocorticoids decrease formation of cerebrospinal fluid, which results in a reduction of intracranial pressure. In human beings, glucocorticoids are believed to influence mood (including "euphoria"), behavior, and brain excitability (Schimmer and Parker, 1995). The euphoric effect commonly recognized in dogs also is likely to reflect differences in glucocorticoid receptors. Steroids, including glucocorticoids, also appear to regulate neuronal excitation. As previously described, dexamethasone inhibits microglial cell proliferation; cortisone also will inhibit proliferation, but at higher doses, through glucocorticoid receptors, but will stimulate proliferation through mineralocorticoid receptors (Tanaka et al., 1997). Glucocorticoids induce glutamine synthetase in both the central and peripheral nervous systems (Shirasawa, 1999). Increased glutamate has been associated with CNS pathology, although the relationship between the two remains controversial (Liu, 1999; Obrenovitch, 1999).

Respiratory System

Glucocorticoids are reported to have "permissive" effects on β_2-receptors, promoting bronchodilation (Barnes, 1989). The effects of glucocorticoids on leukotrienes, platelet activating factor, and other mediators important in the pathogenesis of respiratory inflammatory diseases are discussed elsewhere (see anti-inflammatory effects, discussed earlier; and Chapter 31).

Alimentary Tract

Glucocorticoids decrease the absorption of calcium and iron from the gastrointestinal tract and increase the absorption of fats. Secretion of gastric acid, pepsin, and trypsin are increased by glucocorticoids. Gastric mucosal cell growth and renewal are reduced by glucocorticoids, and mucus production is decreased, resulting in compromise of the protective barrier of the gastric mucosa. Collectively these effects contribute to increased susceptibility to gastric ulceration. A retrospective study in humans found 5% developed gastric mucosal lesions while receiving glucocorticoids, particularly patients with rheumatoid arthritis and collagenosis (Horcicka, 1990). It is not clear whether the effects of glucocorticoids on the gastric mucosa occur as a result of impaired mucosal prostaglandin synthesis, although failure of misoprostol (PgE) to protect against glucocorticoid-induced ulceration indicates not. Indeed, some studies have shown that glucocorticoids provide a gastroprotective effect during stress-induced ulceration (Filaretova, 1999). Deposition of glycogen in the liver, resulting in hepatomegaly in animals chronically treated with glucocorticoids, is a consequence of increased glycogen synthesis as described previously. Cortisol excess can induce pancreatic ductule hyperplasia.

Reproduction

Glucocorticoids can induce parturition during the latter stages of pregnancy in ruminants and horses, but their effect in dogs and cats has not been determined. Glucocorticoid administration to the dog has been associated with cleft palate and abortion. Glucocorticoids have been shown to inhibit cell division, DNA synthesis, or both in the developing liver, lung, brain, and thymocytes.

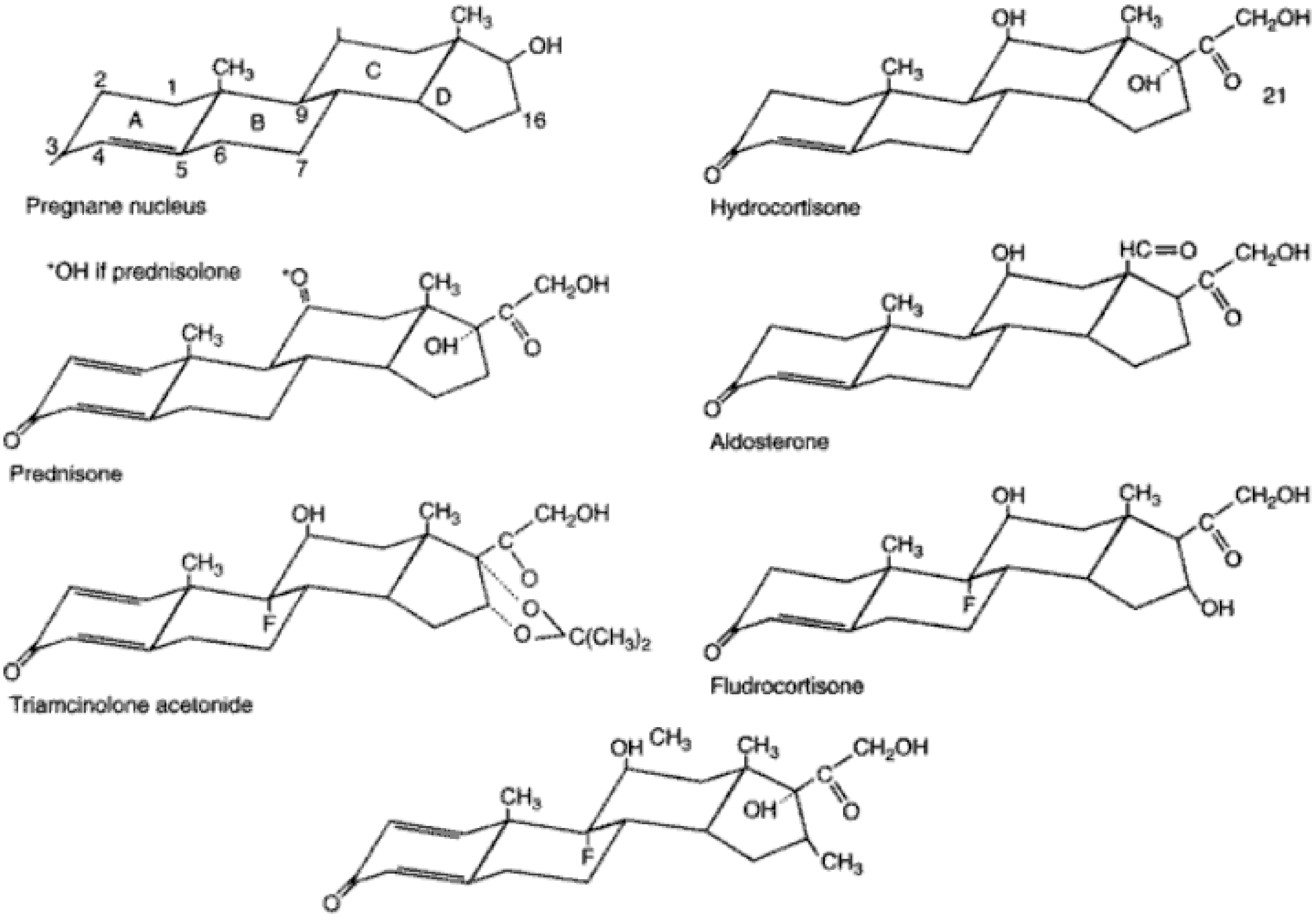
STRUCTURE-ACTIVITY RELATIONSHIP

There are close to 50 different generic corticosteroid products available approved for human use and several approved for use in small animals. These drugs differ primarily in their duration of action, mineralocorticoid activity, and anti-inflammatory potency. As the anti-inflammatory potency of a particular agent increases, its biologic half-life and duration of action also increase. Anti-inflammatory properties parallel the effects on carbohydrate and protein metabolism, but mineralocorticoid effects can be altered independently by changing the molecular structure of the steroid (Fig. 17–5). The 4,5 double bond and the 3-ketone are necessary for mineralocorticoid and glucocorticoid effects. Addition of a 1,2 double bond increases the ratio of glucocorticoid to mineralocorticoid effects and increases the duration of action. Fluorination at the C-9 position increases both mineralocorticoid and glucocorticoid potencies, and methylation at the C-16 position eliminates mineralocorticoid activity.

CLINICAL PHARMACOLOGY

Absorption

Several products are well absorbed orally. For intramuscular administration, the duration and onset of action of a



Pregnane nucleus

Hydrocortisone

*OH if prednisolone

Prednisone

Aldosterone

Triamcinolone acetonide

Fludrocortisone

Dexamethasone

Figure 17–5. Chemical structures of selected adrenocorticosteroids. The pregnane nucleus provides the skeletal structure of corticosteroids. Corticosteroid activity depends on the double bond at position 4,5 and the keto group in the 3 position. Compounds with a double bond at position 1,2 have increased glucocorticoid activity (e.g., prednisone vs. hydrocortisone) as well as a longer duration of action. Prednisolone differs from prednisone only by the presence of a hydroxyl rather than a ketone group on the C ring. A methyl group at the C-16 position eradicates mineralocorticoid activity (e.g., dexamethasone). Fluorination at the C-9 position enhances corticosteroid potency. The addition of acetate rather than succinate esters (not shown) to the various compounds also prolongs duration of action.

particular glucocorticoid can be altered by the addition of an ester, usually bound to C-21. The glucocorticoid esters must be hydrolyzed to release the active, free form of the drug. The sodium phosphate and sodium succinate esters are water soluble, can be administered intravenously, and are rapidly hydrolyzed. These characteristics make them ideal for treatment of acute conditions. The acetate, acetonide, valerate, and dipropionate esters are water insoluble and release the active steroid very slowly, providing glucocorticoid activity for days to weeks (i.e., repositol or "depo" products). The major advantage of these esters is convenience of administration. Administration at 2- to 6-week intervals, depending on the preparation used and disease being treated, has been recommended. Disadvantages include unpredictability of blood concentrations, chronic suppression of the hypothalamic-pituitary-adrenal axis (up to 12 weeks or more following administration of a single dose), possible induction of steroid resistance (mediated by receptor down-regulation), and the fact that the drug cannot be withdrawn should adverse reactions develop. For these reasons, the authors recommend the use of short-acting to intermediate-acting preparations administered daily or on alternate days over repositol steroid preparations.

There are many forms of glucocorticoids available for topical use, including extensions of the skin such as the external ear canal and anal sacs. Once absorbed through the skin, topical corticosteroids are handled by the body in the same capacity as systemically administered glucocorticoids. The extent of percutaneous absorption of topical glucocorticoids depends on factors such as the vehicle, the ester form of the steroid (greater lipid solubility enhances percutaneous absorption), duration of exposure, surface area, and the integrity of the epidermal barrier. Ointment bases are occlusive and are therefore more likely to increase percutaneous absorption of the same glucocorticoid in a cream base. Highly potent preparations in any form should not be used on abraded skin.

Glucocorticoids are absorbed and can achieve physiologic and possibly pharmacologic concentrations after local administration. This includes the skin, as previously noted, synovial spaces, conjunctival sac, and the respiratory tract (Schimmer and Parker, 1995). Suppression of the HAA axis has been documented after ocular (Roberts, 1984) and topical (Zenoble, 1987) administration for several weeks.

Distribution, Metabolism, and Excretion

In humans (and presumably many animals), endogenous (and exogenous) cortisol is bound to corticosteriod-binding globulin (transcortin). This α-globulin is secreted by the liver. Whereas it has a high affinity for steroids, it has a relatively low binding affinity. Albumin, which has a low affinity but large binding capacity, also binds glucocorticoids. Corticosteroids compete with one another (endogenous and exogenous) for binding sites and at high concentrations will displace one another. Steroidal hormones tend to be eliminated by oxidation or reduction followed by conjugation (generally glucuronide or sulfate) and excretion (principally renal). Metabolism occurs at both hepatic and extrahepatic (including the kidney) sites. The importance of 11β-hydroxysteroid hydrogenase in determining aldosterone-responsive tissues was previously addressed. Biliary and fecal elimination do not appear to be that significant (Schimmer and Parker, 1995).

PREPARATIONS

Knowledge of a few commercial preparations is sufficient for most clinical purposes (see Table 17–2). Selection is most commonly based on balancing the need for efficacy with the risk of adverse effects. Some distinct characteristics of selected steroids are presented here.

Hydrodrocortisone

Hydrocortisone is identical to cortisol, the most important endogenous glucocorticoid for most species. Because of the short duration of action (<12 hours) and low potency of hydrocortisone, it is not frequently used for systemic therapy. Hydrocortisone is available in creams and ointments for topical use.

Prednisolone and Prednisone

Prednisone is rapidly metabolized by the liver to prednisolone (C-11 ketol reduction). Liver disease probably has minimal effect on activation. Prednisolone has an intermediate duration of action (12 to 36 hours) and is therefore ideal for alternate-day administration.

Methylprednisolone

Methylprednisolone possesses lipid antioxidant activity that has been shown to be beneficial in the treatment of experimental spinal cord trauma in cats and experimentally induced *E. coli* bacteremia (Arvidsson et al., 1990; Means, 1981). In contrast, methylprednisolone did not appear clinically beneficial in a canine model of spinal trauma, although the model may have caused insufficient damage for effective evaluation (Coates, 1995). Although some other glucocorticoids (dexamethasone, prednisolone) are efficacious as lipid antioxidants, methylprednisolone is the most potent. Methylprednisolone has an intermediate duration of action (12 to 36 hours) and is also a good candidate for alternate-day administration.

Dexamethasone

Dexamethasone is a highly potent glucocorticoid but has virtually no mineralocorticoid activity. It possesses some lipid antioxidant activity. The prolonged duration of action (biologic half-life approximately 48 hours) of dexamethasone makes it inappropriate for alternate-day administration.

Table 17–3. Inflammatory and Immune Responses Impacted by Glucocorticoids

Targeted Cell	Targeted Effect	Glucocorticoid Effect
Macrophages/ monocytes	Antigen processing	Impaired
	Prostaglandins and leukotrienes and related compounds; platelet-activating factor	Lipocortin-mediated inhibition of phospholipase$_2$-mediated release of substrate (arachidonic acid)
	Cytokines (IL-1, IL-6, TNF-α)	Inhibition of production and release
	Acute phase reactants	Impaired complement function
Neutrophils	Adhesion, cytotoxic actions	
Basophils	Histamine, serotonin, arachidoninc acid metabolites (preformed and in situ mediators of inflammation)	Decreased degranulation, decreased formation of metabolites
Eosinophils		
Lymphocytes	Cytokines (IL-1, IL-2, IL-3, IL-6, TNF-α, GM-CSF, IFN-γ)	Inhibition of production and release
Fibroblasts	Arachidonic acid metabolites	Impaired synthesis (see macrophages)
	DNA synthesis, fibroblast proliferation (induced by growth factor)	Inhibited
Endothelial cells	Adhesion molecules (ELAM-1, ICAM-1)	Decreased leukocyte localization
	Acute phase reactants	Impaired complement function
	Arachidonic acid metabolites	Impaired synthesis (see macrophages)
	Cytokines	Inhibition of production and release

Abbreviations: ELAM-1 = endothelial leukocyte adhesion molecule; GM-CSF = granulocyte/macrophage colony-stimulating factor; ICAM = intracellular adhesion molecule; IFN = interferon; IL = interleukin; TNF = tumor necrosis factor.

Betamethasone

Betamethasone is a very potent glucocorticoid that varies from dexamethasone only in the orientation of a side chain. Thus, like dexamethasone, it has virtually no mineralocorticoid activity. It has a long duration of action (biologic half-life approximately 48 hours) and is therefore not appropriate for alternate-day administration.

Beclomethasone

Beclomethasone is a glucocorticoid characterized by high first-pass metabolism and thus low systemic bioavailability. The drug is used as an inhaled product for treatment of human asthma.

Tirilazad Mesylate

Tirilazad mesylate is a novel, nonglucocorticoid, 21-aminosteroid (lazaroid) that possesses potent antioxidant activity (i.e., protects against oxygen-derived free radicals). Unlike the glucocorticoids, this agent does not inhibit phospholipase A_2, but it does inhibit lipid peroxidation-induced arachidonic acid release (Brown and Hall, 1992). The mechanism appears to reflect, in part, insertion into the cell membrane (see Fig. 16–12, p. 307). These products are discussed in depth in Chapter 16.

Fludrocortisone

Fludrocortisone is a synthetic steroid hormone with mineralocorticoid (no glucocorticoid) activity only. Fludrocortisone acetate is administered orally at 24- to 48-hour intervals for treatment of hypoadrenocorticism.

Desoxycorticosterone Pivalate

Desoxycorticosterone pivalate (DOCP) is an ester salt of a synthetic steroid hormone with mineralocorticoid (no glucocorticoid) activity. This form of desoxycorticosterone possesses a 20- to 30-day duration of action after intramuscular injection. Addisonian patients who have failed to completely respond to fludrocortisone may respond to therapy with DOCP. Currently, DOCP has been approved through CIBA-Geigy.

THERAPEUTICS

Unless one is administering glucocorticoids for replacement therapy in a deficiency state (i.e., hypoadrenocorticism), glucocorticoid therapy is not directed at the inciting agent. Glucocorticoid therapy is intended to reduce the physiologic processes that are activated in response to the disease (Table 17–3). In general, an anti-inflammatory dose is considered to be 10 times the "physiologic" dose, and immunosuppressive doses are twice the anti-inflammatory dose. Shock doses of glucocorticoids are 5 to 10 times the immunosuppressive dose. When treating a patient for an immediately life-threatening condition such as shock or cerebral edema, large doses of glucocorticoids should be used. Similarly, autoimmune diseases such as immune-mediated hemolytic anemia should be treated aggressively. Therapy should be initiated and continued with an immunosuppressive dose until consistent improvement in the patient's status is observed. Because high doses of glucocorticoids are often required to adequately treat immune-mediated diseases, adverse effects are likely to occur. Concurrent administration of additional immunosuppressive drugs (azathioprine, cyclophosphamide) may allow the glucocorticoid dose to be decreased. Dose reduction in patients with autoimmune diseases should be conducted gradually. The reduced dose should be continued for at least 2 weeks before the next attempted dose reduction, and the actual dose should be decreased by no more than half. It is essential to assess the patient's status frequently for recurrence of clinical signs.

Conversely, the smallest dose that will achieve the desired effect should be used if glucocorticoids are to be administered for relatively benign, chronic, inflammatory conditions such as atopy or flea allergy dermatitis. This dose is determined by trial and error and must be reevaluated from time to time. Periodically, an attempt should be made to reduce the dose. An every-other-day dosage regimen with a short-acting or intermediate-acting agent can achieve therapeutic effects without untoward effects in many patients. Agents that are ideal for alternate-day administration include prednisone, prednisolone, and methylprednisolone. The duration of action of hydrocortisone and cortisone may be too short for effective alternate-day therapy. Although triamcinolone's duration of action is similar to those of prednisolone and methylprednisolone, its ability to suppress the hypothalamic-pituitary-adrenal axis is more typical of the long-acting agents such as dexamethasone and betamethasone. Concurrent treatment with nonglucocorticoid antipruritics such as antihistamines or fatty acid supplements should be attempted in order to reduce the glucocorticoid dose (Miller and Scott, 1994).

Side effects can occur if withdrawal of a glucocorticoid occurs too rapidly. In human patients receiving glucocorticoids, the most frequent problem encountered with rapid withdrawals is recrudescence of the underlying condition for which the glucocorticoid was indicated (Schimmer and Parker, 1995). The most severe but rare complication, however, is acute adrenal insufficiency. Because of variability in glucocorticoid impact on the hypothalamic adrenal axis and variability within and between animals, predicting which animal is likely to develop insufficiency is difficult. In general, iatrogenic Addison disease is not common, but even this risk can be minimized by gradual withdrawal of the glucocorticoid. In human patients, those who receive supraphysiologic doses for 2 weeks within the preceding year are considered to have some level of hypothalamic-pituitary-adrenal suppression (Schimmer and Parker, 1995).

THERAPEUTIC INDICATIONS

Dermatologic

Glucocorticoids are the cornerstone of therapy of many of the autoimmune diseases affecting the skin, including the pemphigus complex, systemic lupus erythematosus, and discoid lupus erythematosus. Optimal therapy for each of these diseases varies, as some may respond to glucocorticoids alone and some may require a combination of glucocorticoids and alternate immunosuppressive drugs such as azathioprine or cyclophosphamide.

The long-term management of canine atopy (allergic inhalant dermatitis) frequently requires the use of glucocorticoids. If at all possible, hyposensitization and avoidance therapy should be attempted before medical management. Although glucocorticoids are the most effective anti-inflammatory/antipruritic medication currently available for the atopic patient, alternate forms of therapy, as previously noted (e.g., antihistamines, misoprostil, omega fatty acids, and combinations thereof), should be attempted before sentencing a patient to chronic glucocorticoid therapy. Initial treatment with prednisolone at an anti-inflammatory induction dose of 0.5 to 1 mg/kg per day is recommended. After resolution of clinical signs, the therapy should be switched to an alternate-day regimen. An effective alternate-day dose can be achieved by taking the lowest effective daily dose and increasing it by 50% (Bevier, 1990). Some dogs may require medication every 3 to 4 days. The use of injectable repositol forms of glucocorticoids is not recommended for treatment of canine atopy.

Atopy is believed to exist in the cat also. There is little information regarding the efficacy of antihistamines and fatty acid supplements as antipruritics in the cat. Glucocorticoids are the therapy of choice for treatment of atopic pruritis in the cat (Carlotti, 1992). As with dogs, short-acting to intermediate-acting compounds (prednisolone 1 to 2 mg/kg per day) are recommended, and alternate-day therapy should be the goal.

Otic

Otitis externa, often occurring as a component of atopy, is frequently responsive to topical glucocorticoid therapy (see Chapter 10). Products usually contain an antibiotic and antifungal in addition to the glucocorticoid, and these agents can help resolve secondary infections. It is important to note that topically administered glucocorticoids can be absorbed systemically (Meyer et al., 1990). Efforts to remove or resolve the inciting factors should be made in cases of chronic otitis externa. More severe otitis externa, such as idiopathic hyperplastic otitis externa of cocker spaniels, may require systemic glucocorticoid treatment (prednisolone at 0.5 to 1 mg/kg per day) (Royschuk, 1994). Follow-up examinations, usually at 2-week intervals, should include otoscopic and cytologic examinations to identify potential complications (otitis media, secondary yeast or bacterial infection, parasites, and so forth). It should be stressed that glucocorticoid therapy is *not* a substitute for thorough cleaning and drying of the ear.

Respiratory

Glucocorticoids have a pivotal role in the treatment of selected respiratory conditions. Their efficacy as bronchodilators (through their permissive effects on β_2-receptors) and as an anti-inflammatory agent has been well documented in patients with asthma. Among clinically used anti-inflammatory drugs, glucocorticoids alone inhibit prostaglandins, leukotrienes, and platelet-activating factor. Their effects on macrophage processing are well documented. These mediators have important roles in the pathophysiology of chronic bronchial disease. In human patients, inhaled glucocorticoids (beclamethasone, triamcinolone) tend to be first-line drugs. In cats suffering from bronchial asthma, glucocorticoids are administered acutely and are the cornerstone of long-term therapy. Preference for the particular drug varies among clinicians. In patients suffering from status asthmaticus, water-soluble preparations of prednisolone tend to be used for their rapid effects, whereas dexamethasone may be preferred because it is more potent and provides a more prolonged effect. A combination of both products might be considered for immediate effects followed by the more prolonged effects. Long-term therapy generally consists of oral forms of prednisolone, although some clinicians may prefer triamcinolone because of its enhanced potency. Alternate-day therapy may, however, be of no benefit for this intermediate-acting to long-acting glucocorticoid.

As with other conditions requiring prolonged therapy, a higher dose is administered initially, with tapering of the dose to a minimal acceptable level. Life-long therapy may be necessary for some cats. The use of repositol steroid preparations is controversial. Although convenient, lack of predictability regarding retreatment may preclude their effective use. In cases of relapse, intravenous administration of dexamethasone or nebulized steroid therapy may be of benefit. Greater discretion is indicated for long-term use of glucocorticoids in chronic respiratory diseases in dogs. Noninfectious diseases associated with eosinophilic or macrophage infiltrates are indications for glucocorticoid therapy, usually in conjunction with bronchodilator therapy. Short-acting glucocorticoids can be used on a short-term basis (<48 hours) to break a cough cycle in patients with upper respiratory syndromes associated with inflammation (i.e., tracheobronchitis).

Musculoskeletal

Understanding the implications of glucocorticoid use for the treatment of osteoarthritis (OA) requires appreciation of the pathophysiology of OA and the effects of glucocorticoids on normal joint physiology. Glucocorticoids have variable and opposite effects on joint physiology, depending on the dose used (Chunekamrai et al., 1989). Low concentrations appear to be chondroprotective, whereas higher concentrations are chondrodestructive.

The term *steroid arthropathy* was coined to refer to the destructive condition that occurs in joints after multiple intra-articular injections of glucocorticoids in human patients (Chunekamrai et al., 1989). In animal models (including dogs), the detrimental effects of glucocorticoids can occur after administration of a single intra-articular injection or multiple systemic doses. In addition to the destruction induced by glucocorticoids on cartilage, indirect damage may occur due to failure to rest an injured joint. Finally, glucocorticoids negatively impact subchondral bone by inhibition of osteoblastic activity.

Despite the obvious role glucocorticoids have in preventing cartilage catabolism and controlling inflammation, their use for the treatment of osteoarthritis is controversial. Although short-term use is generally accepted for acute conditions or trauma, long-term use is less acceptable. Much of the controversy might be resolved if a "physiologic dose" could be defined. In a canine model of OA, an oral dose of 0.2 to 0.25 mg/kg per day prednisone or an intra-articular dose of 5 mg per month triamcinolone hexacetonide significantly reduced the incidence and severity of cartilage lesions and osteophyte formation (Pelletier and Martel-Pelletier, 1989). The advantages of intra-articular administration include minimization (but not total avoidance) of systemic effects. Disadvantages include the potential need for chemical restraint and the risk of sepsis.

Newer glucocorticoids characterized by increased anti-inflammatory potency yet decreased negative effects on cartilage may resolve the controversy regarding the use of glucocorticoids in the treatment of OA. Until these drugs are available, or a "physiologic dose" has been established, the authors recommend reservation of glucocorticoids in the treatment of OA to the animal that has failed to respond to chondroprotective agents or nonsteroidal anti-inflammatory agents that are chondroprotective. Concurrent use of glucocorticoids and nonsteroidal anti-inflammatory agents enhances the risk for gastrointestinal ulceration and should be avoided. Finally, if glucocorticoids are used, low doses (as noted above) should be administered, and the simultaneous use of disease-modifying chondroprotective agents should be considered.

Central Nervous System

Glucocorticoids are used for treatment of both brain and spinal cord disease. Their beneficial effects include protection from free radicals, reduction in intracranial pressure (decreased production of cerebrospinal fluid), and maintenance of normal microvasculature integrity. Glucocorticoids appear to be beneficial in reducing or preventing cerebral edema associated with neoplasia; however, cerebral edema caused by trauma is thought to be less responsive to glucocorticoid therapy.

There is increasing evidence that lipid peroxidation, and resultant formation of oxygen-derived free radicals, plays an important role in tissue damage subsequent to brain or spinal cord trauma. Several glucocorticoids, including methylprednisolone (most potent), dexamethasone, and prednisolone, are capable of inhibiting lipid peroxidation (Brown and Hall, 1992). Their ability to inhibit phospholipase A_2 may also protect injured nervous tissue. For treatment of acute CNS injury, the water-soluble salts should be used. Recommended dosage regimens for these agents in the treatment of CNS injury in dogs and cats are methylprednisolone sodium succinate 30 mg/kg intravenous (IV), followed by 15 mg/kg 2 and 6 hours later, and then 2.5 mg/kg per hour for the first 48 hours; prednisolone sodium succinate 60 mg/kg IV, followed by 30 mg/kg 2 and 6 hours later, and then 5 mg/kg per hour for the first 48 hours; dexamethasone sodium phosphate 4 mg/kg IV every 6 hours for the first 48 hours (Brown and Hall, 1992). In studies involving cats with spinal cord injury, methylprednisolone sodium succinate–treated cats had significantly improved neurologic outcome, while the neurologic outcome of cats treated with dexamethasone was not significantly different than placebo (Hoerlein et al., 1983, 1985).

Noninfectious, or so-called steroid responsive, meningitis and granulomatous meningoencephalitis are diseases that frequently respond dramatically to glucocorticoid therapy. Prednisolone at a dose of 2 to 4 mg/kg per day has been recommended.

Inflammatory Bowel and Liver Disease

Inflammatory bowel disease in cats (especially those with lymphocytic-plasmacytic infiltrates) is frequently responsive to prednisolone at 2.2 mg/kg per day (Tams, 1992). For more severe cases, dexamethasone at 0.22 mg/kg per day plus metronidazole may be effective. In either case, the initial dose should be maintained for 2 weeks beyond the time that the cat's clinical signs begin to resolve. Cats that respond immediately should receive the initial dose for at least 4 weeks before dose reduction is attempted.

Inflammatory bowel disease in dogs may be less responsive to glucocorticoid therapy than is the case in cats (canine patients with eosinophilic infiltrates are an exception). Initial treatment of lymphocytic-plasmacytic enteritis and colitis is with prednisolone 2.2 mg/kg per day. Frequently, additional therapy is necessary (metronidazole, azathioprine). In all cases, dietary modification should accompany pharmacologic therapy. Alimentary lymphosarcoma should be ruled out before steroid therapy (especially in cats).

Corticosteroid therapy for liver disease remains somewhat controversial. Clinical studies in human medicine have shown that steroid therapy in chronic active hepatitis improves survival rates. Nonsuppurative cholangitis/cholangiohepatitis may respond to immunosuppressive glucocorticoid therapy.

Gingivitis and Stomatitis

The eosinophilic granuloma complex in cats is usually responsive to high-dose glucocorticoid therapy such as methylprednisolone acetate 20 mg intramuscularly every 2 to 3 weeks for three treatments. Lymphocytic-plasmacytic gingivitis and stomatitis in cats may respond to glucocorticoid therapy (prednisone 2 to 4 mg/kg orally every 24 hours).

Shock

Septic Shock (see also Chapter 10)

The use of glucocorticoids in septic shock are controversial despite the recognition of their potential benefits as early as 1951 (Lefering and Neugebauer, 1995; Hardie, 1990). Evidence varies with experimental versus clinical studies. Experimental models of septic shock have shown glucocorticoids to be of benefit if administered before or concurrently with endotoxin administration (i.e., within the first 2 hours). In canine models, severe mesenteric vasoconstriction within the first 15 minutes can lead to irreversible shock. Thus, it is unlikely that glucocorticoids will provide beneficial effects if they are administered 30 to 60 minutes after administration of the endotoxin (Haskins, 1982). One of the differences between results of experimental versus clinical (spontaneous) models of septic shock may be the choice of outcome measures. Often, survival in experimental models is based on short-term analysis (i.e., survival for several hours). In addition, clinically, the likelihood of knowing the time of onset of endotoxemia or sepsis is extremely low.

The use of glucocorticoids for human patients suffering from sepsis and septic shock was addressed in a large meta-analysis of human clinical trials (Lefering and Neugebauer, 1995). In this study, 10 of 49 published reports investigating the effects of corticosteroids in septic shock human patients were considered to be the "best" based on scientific design (e.g., controlled, blinding techniques, and so forth). Even within these 10 studies, however, differences in experimental design, definition of septic shock, drugs, dosing regimens, and timing of steroid administration and other design considerations limited the number of conclusions that could be made. Mortality rates often were the basis of analysis; however, mortality was not determined at the same time in all 10 studies. Yet, information provided by the analysis might be relevant to veterinary patients. Of the 10 studies examined, only one study offered a significant positive effect for patients receiving glucocorticoids. Most studies show a beneficial effect of steroids during the first few hours after the initiation of shock. Low dose versus high dose appeared to be unimportant in determining survival or response. Different drugs did not seem to make a difference, although only dexamethaxone and methylprednisolone were studied in more than one trial. Patients with sepsis associated with gram-negative infections demonstrated a slightly better outcome. The most common or severe side effects after steroid treatment was gastrointestinal bleeding (reported in five studies), although administration for 6 days appeared to be the major reason this side effect was important. Superinfection (secondary infection) was reported in 7 of the 10 studies. The concern of secondary infection in dogs suffering from sepsis or septic shock also has been expressed in the veterinary literature (Hardie, 1990). Lefering and Neugebauer (1995) concluded that the broad use of corticosteroids in patients with sepsis or septic shock "is not beneficial" and that a new trial would not be indicated. They also agreed, however, that short-term, high-dose treatment is not associated with an increased risk of complications. The authors recognize that very early initiation (or prophylactic use) of steroid therapy in gram-negative infections may reduce the generalized inflammatory response to infection (Lefering and Neugebauer, 1995).

The use of glucocorticoids in dogs or cats in sepsis or septic shock might be approached in a similar manner. Should glucocorticoids be used, rapid-acting, water-soluble agents such as dexamethasone sodium phosphate (4 to 8 mg/kg, IV), prednisolone sodium succinate or sodium phosphate (30 mg/kg, IV), or methylprednisolone sodium succinate (30 mg/kg, IV) are preferred. Shock doses of glucocorticoids are 5 to 10 times the immunosuppressive dose. Short-term administration (one to two doses) should be considered.

Hemorrhagic Shock

The use of glucocorticoids for treatment of hemorrhagic shock is controversial. Some studies in dogs suggest that dexamethasone sodium phosphate (5 mg/kg, IV) may improve blood flow to the kidneys, lungs, and gastrointestinal tract (Papich and Davis, 1989). Other supportive measures, particularly aggressive fluid therapy, must also be instituted. Appropriate fluid replacement therapy ensures adequate drug distribution to target tissues.

Neoplasia

Prednisolone is often included in combination chemotherapy protocols for treatment of lymphoma and multiple myeloma for their cytotoxic actions. The use of glucocorticoids as a single agent for treatment of lymphoma can rapidly induce multiple drug resistance in the neoplastic cells. When this occurs, the tumor will fail to respond not only to prednisolone but also to other chemotherapeutic agents (doxorubicin, vincristine) as well. For this reason, single-agent chemotherapy of lymphoma with prednisolone is not recommended. Glucocorticoids are often used in patients with mast cell tumors to decrease the inflammatory response associated with mast cell degranulation. Additionally, glucocorticoids may induce a partial or complete remission in some canine patients with mast cell tumors (McCaw et al., 1994).

Ophthalmologic

Topical glucocorticoid therapy is efficacious for treatment of noninfectious conjunctival, scleral, corneal, and anterior uveal inflammatory diseases. Before topical corticosteroid use, however, the corneal epithelium should be examined (via fluorescein dye) for the presence of corneal ulceration. The presence of corneal ulceration precludes the use of topical corticosteroids. Prednisolone acetate penetrates the intact corneal epithelium and is therefore effective for treatment of intraocular inflammation (Davidson, 1989). Systemic absorption of topical ophthalmic corticosteroids has been documented in dogs. Systemic glucocorticoid therapy is necessary for treatment of noninfectious posterior segment inflammatory conditions.

Hematopoietic

Glucocorticoids are the mainstay, first-line therapy for both immune-mediated hemolytic anemia and thrombocytopenia. There is anecdotal evidence that initial treatment with dexamethasone may be superior to prednisone therapy, but no controlled studies have substantiated this claim. Prednisone (2 to 4 mg/kg per day) or dexamethasone (0.3 to 0.6 mg/kg per day) therapy should be continued until erythrocyte or platelet numbers steadily increase. Subsequently, the dose should be slowly (over 3 to 6 months) tapered. Addition of glucocorticoids is also beneficial for treatment of immune-mediated neutropenia and for treatment and prevention of transfusion reactions.

Hypoadrenocorticism

An addisonian crisis requires treatment with rapid-acting glucocorticoids and mineralocorticoids. Not all synthetic glucocorticoids are effective for replacement of mineralocorticoid deficiency. Dexamethasone, methylprednisolone, triamcinolone, and betamethasone are virtually devoid of mineralocorticoid activity. For treatment of acute hypoadrenocorticism, if a mineralocorticoid such as fludrocortisone (Florinef) or DOCP is unavailable, prednisone or cortisone may provide adequate mineralocorticoid activity.

ADVERSE EFFECTS

Adverse reactions resulting from glucocorticoid therapy can occur through either cessation of therapy or prolonged use. Acute adrenal insufficiency results from rapid withdrawal of glucocorticoids after prolonged treatment (see earlier discussion of clinical use). Termination of glucocorticoid therapy in a chronically treated patient should be performed gradually over several months. Complete recovery of the hypothalamic-pituitary-adrenal axis may require 9 months. During this time, patients may need supplemental glucocorticoids under "stressful" situations (e.g., surgery).

Complications of glucocorticoids related to prolonged therapy are described later. In general, dogs are more susceptible to these complications than are cats. The incidence of adverse effects resulting from glucocorticoid administration is frequently related to the dose and duration of treatment. Alternate-day therapy with short-acting preparations can significantly reduce the incidence of adverse reactions.

Central Nervous System

Glucocorticoids induce polyphagia in dogs and to a lesser degree in cats. This may contribute to the development of obesity in some patients but may stimulate the appetite of an anorexic patient. Changes in mood or behavior have been noted in human patients treated with glucocorticoids. Although these are more difficult to document in veterinary patients, most clinicians have noted positive attitude changes in patients being treated with glucocorticoids.

Musculoskeletal

Muscle weakness and muscle atrophy are commonly observed in dogs with hyperadrenocorticism and dogs receiving large doses of glucocorticoids (see previous discussion). These effects in part reflect muscle wasting that may result from the catabolic gluconeogenic effects of glucocorticoids.

Glucocorticoids are associated with osteoporosis and vertebral compression in 30% to 50% of human patients receiving the drugs chronically. Mechanisms include direct inhibition of osteoblasts (decreased bone formation), inhibition of calcium absorption from the intestines, increased parathormone secretion, which in turn increases osteoclast-mediated bone resorption, and increased calcium excretion (Schimmer and Parker, 1995). Osteoporosis is not a clinically recognized entity in small animals receiving glucocorticoids, in part because of differences in body posture as well as duration of therapy. Prudence is indicated, however, when glucocorticoids are used in the face of conditions that facilitate or are facilitated by the negative sequelae of glucocorticoids on bone formation. Aseptic necrosis has been reported in human patients after a short course of high doses of glucocorticoids (Schimmer and Parker, 1995).

Gastrointestinal and Liver

The likelihood of glucocorticoids causing gastrointestinal ulceration is controversial. In general, patients that develop ulceration are predisposed to ulceration due to stress or are receiving other drugs that contribute to gastrointestinal damage, most notably nonsteroidal anti-inflammatory drugs. In stressed animals, peripheral effects of centrally or peripherally mediated norepinephrine may be important to the manifestation of gastrointestinal ulceration mediated by glucocorticoids (Bakke et al., 1986). Colonic perforation in dogs with spinal cord injuries has been associated with the use of dexamethasone, perhaps in part due to modulation of local blood flow. Pancreatitis has been associated with the use of glucocorticoids alone and in combination with azathioprine. Glucocorticoids can induce hepatocellular swelling due to fat, glycogen, or water accumulation. Clinically these changes are seen as hepatomegaly and elevated liver enzyme activity. In dogs, induction of a steroid-induced alkaline phosphatase isoenzyme occurs in patients receiving glucocorticoids.

Metabolic

Glucose intolerance, insulin resistance, overt diabetes mellitus, and hyperlipidemia can be induced in canine patients receiving glucocorticoid therapy.

Endocrine

Exogenous administration of glucocorticoids suppresses the hypothalamic-pituitary-adrenal axis via feedback inhibition on the anterior pituitary and the hypothalamus. Chronic suppression of the axis can result in iatrogenic hypoadrenocorticism on discontinuation of exogenous glucocorticoids.

Glucocorticoids cause a decrease in plasma concentrations of total triiodothyronine, thyroxine, and thyroid-stimulating hormone, with a normal free triiodothyronine and thyroxine concentration (Feldman and Nelson, 1987b). Therefore, when assessing thyroid function in animals receiving glucocorticoids, their influence on total thyroid hormone concentrations should be kept in mind. Glucocorticoid administration does not result in clinical hypothyroidism because the free hormone concentration is minimally affected. Glucocorticoids increase parathormone secretion.

Renal

Polyuria and polydipsia are classically associated with glucocorticoid excess (either endogenous or exogenous). Several factors probably contribute to this effect, including increased glomerular filtration rate due to increased vascular volume, increased renal calcium excretion, inhibitory actions on antidiuretic hormone, and direct actions decreasing permeability of the distal tubule.

Cardiovascular

Many human patients receiving glucocorticoids develop hypertension as a result of sodium retention. Hypertension occurs in dogs with hyperadrenocorticism and presumably could in veterinary patients receiving exogenous glucocorticoids also. Postulated mechanisms for hypertension in canine hyperadrenocorticism include increased activation of angiotensin I, increased vascular responsiveness to catecholamines, and reduction of vasodilator prostaglandins.

Immune Function

Glucocorticoid therapy is associated with an increased risk of bacterial, viral, and fungal infection, although this effect is dose dependent. A single dose of a short-acting to intermediate-acting glucocorticoid is unlikely to significantly suppress immune function. Chronic administration of glucocorticoids can result in recurrent cystitis, septicemia, and endocarditis. This does not, however, justify the routine use of antimicrobials to "cover" the patient in order to avoid bacterial infection. A bactericidal antimicrobial agent selected on the basis of culture and sensitivity results should be used in the case of a documented bacterial infection.

Respiratory

Pulmonary thromboembolism is a potential complication of hyperadrenocorticism and presumably can occur with excess exogenous glucocorticoids also. The exact pathophysiologic mechanism is unknown but may be a result of obesity, hypertension, increased hematocrit, or hypercoagulability. In addition, because of the myopathic effect of glucocorticoids, muscles of respiratory function may be weakened in animals receiving high doses of glucocorticoids (Schimmer and Parker, 1995).

Growth Retardation

The administration of small doses of glucocorticoids to children has been associated with retardation of growth. The mechanism may reflect changes in collagen synthesis but are likely to be much more complex. Prepartum exposure to glucocorticoids can predispose experimental animals to malformations (e.g., cleft palate).

CONTRAINDICATIONS

Glucocorticoids produce profound actions on virtually all systems of the body. Many of these effects can be tolerated by a healthy animal, but in certain disease states the use of glucocorticoids may be deleterious. Those diseases and conditions that the authors consider to be major, moderate, and minor contraindications to glucocorticoid therapy are mentioned.

Infectious Disease

Infectious diseases are a major contraindication. Glucocorticoids can exacerbate viral, bacterial, and fungal infections due to their immunosuppressive properties (although a single anti-inflammatory dose of a short-acting agent is unlikely to be harmful).

Diabetes Mellitus

Diabetes mellitus is a major contraindication. Glucocorticoid-mediated gluconeogenesis and general anti-insulin effects make it extremely difficult to regulate diabetic patients.

Renal Failure

Renal failure is a moderate contraindication. Increased protein catabolism induced by glucocorticoids results in increased quantities of nitrogenous waste products to be excreted. Additionally, patients with renal failure are already immunocompromised. Further immunosuppression would greatly increase the risk of developing pyelonephritis.

Corneal Ulceration

Corneal ulceration is a major contraindication. Topically administered glucocorticoids delay healing of the cornea and may lead to corneal perforation.

Pancreatitis

Pancreatitis is a moderate contraindication. Glucocorticoids are believed to aggravate pancreatitis by increasing fatty acid circulation.

Gastrointestinal Ulceration

Gastrointestinal ulceration is a moderate contraindication. Glucocorticoids promote progression of ulcerative disease by delaying healing, increasing acid and pepsin secretion, and reducing the rate of mucosal cell proliferation in the gastrointestinal tract. Patients with eosinophilic enteritis, lymphocytic-plasmacytic enteritis, and certain ulcerative and granulomatous enteritides are potential exceptions. Colonic ulceration is a significant risk in animals with spinal trauma that are receiving dexamethasone. Concurrent nonsteroidal anti-inflammatory drug administration greatly increases the likelihood of gastrointestinal ulceration and is *not* recommended. Misoprostil, a prostaglandin E_2 analogue, may provide protection against glucocorticoid-induced gastric ulceration.

Pregnancy

Pregnancy is a moderate contraindication. Glucocorticoid administration has been associated with abortion and cleft palate in the dog. Additionally, glucocorticoid administration to a bitch within 24 hours of parturition reduces neonatal intestinal permeability of immunoglobulins, thereby reducing colostrum absorption (Gillette and Filkins, 1966).

Epilepsy

Epilepsy is a moderate contraindication. Endogenous glucocorticoids suppress neuronal excitability perhaps by potentiating the inhibitory effects of the neurotransmitter γ-aminobutyric acid. Chronic glucocorticoid use has been reported to be associated with lowering the seizure threshold. The mechanism for this possible effect is not clear. Exogenous glucocorticoids may, however, down-regulate steroid receptors, resulting in increased neuronal excitability.

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18 Chemotherapy

Claudia L. Barton

> "Throughout the centuries the sufferers of this disease have been the subject of almost every conceivable form of experimentation. The fields and forests, the apothecary shop and temple have been ransacked for some successful means of relief from this intractable malady. Hardly any animal has escaped making its contribution in hide or hair, tooth or toenail, thymus or thyroid, liver or spleen in the vain search for a means of relief."
>
> BAINBRIDGE
> *The Cancer Problem, 1914*

INTRODUCTION
COMMON SIDE EFFECTS OF CHEMOTHERAPY
DRUGS USED IN CANCER CHEMOTHERAPY
Alkylating Agents
  Cyclophosphamide
  Melphalan (Phenylalanine Mustard)
  Chlorambucil
  Nitrosoureas
  Dacarbazine
Mitotic Inhibitors: Vinca Alkaloids
Antitumor Antibiotics
  Doxorubicin
  Doxorubicin Analogues
  Dactinomycin (Actinomycin D)
  Bleomycin
  Mitoxantrone
Antimetabolites
  Methotrexate
  Cytosine Arabinoside
  5-Fluorouracil
  Hydroxyurea
Platinum Drugs
  Cisplatin
  Carboplatin
Miscellaneous Drugs
  L-Asparaginase, Pegaspargase
  Piroxicam
  Corticosteroids

INTRODUCTION

Before appropriate treatment for a particular cancer can be instituted, the tumor must first be diagnosed by cytology or histopathology. Testing is then conducted to allow *staging* of the tumor—to determine if there is clinically visible evidence of metastatic spread. Lymph node cytology or biopsy, radiographs, ultrasound examinations, and computed tomographic or magnetic resonance imaging scans may be used as staging procedures. Finally, the biologic behavior typical for the cancer must be considered. If, as a rule, the tumor remains localized, surgery or radiation therapy—or a combination of the two—may be the best way to obtain cure or control. If the tumor is likely to metastasize by lymphatics or hematogenously, however, some form of systemic therapy must be added to make a cure more likely. Systemic therapy involves the administration of biologic agents, hormones, or cytotoxic chemotherapy. Theoretically, cancer chemotherapy is given to kill or suppress the growth of malignant cells without killing normal cells; in fact, however, most of the commonly used drugs are capable of killing both normal and malignant cells, depending on the dose administered. To be useful in clinical practice, an antineoplastic drug must possess selective toxicity—in other words, it should be more toxic to cancer cells than to the normal host cells at conventional doses. This chapter addresses the cytotoxic agents commonly used in the treatment of cancer in dogs and cats.

Drugs used in chemotherapy cause their anticancer effects by interacting with important substrates or enzymes that are related to DNA synthesis or function. Therefore, most anticancer drugs are ineffective against cells that are not actively proliferating. Tumors with a high mitotic index are much more likely to be sensitive to chemotherapy than those in which mitotic activity is low. Because chemotherapeutic drugs are effective principally on cells that are actively replicating, it is important to have an understanding of the phases of the cell cycle before discussion of individual drugs (Fig. 18–1). The part of the cell cycle in which active mitosis occurs has been termed the "M" phase; it is quite short in all cells, generally lasting less

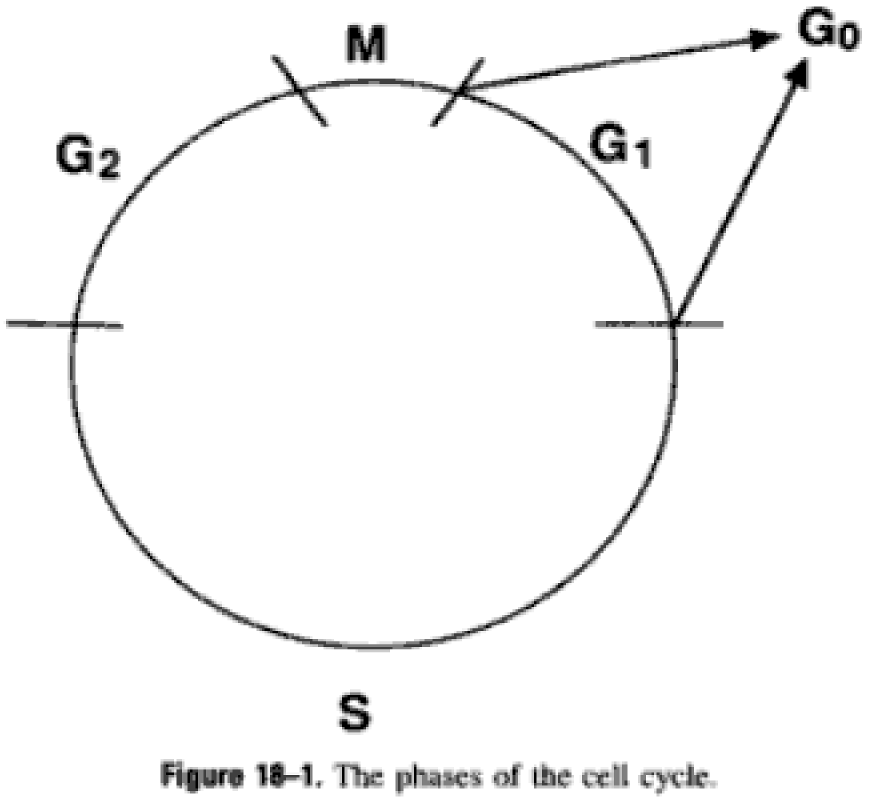

Figure 18–1. The phases of the cell cycle.

than 1 hour. The period during which DNA synthesis occurs for chromosome doubling in preparation for mitosis is called "S" and ranges from 8 to 30 hours. When scientists began to learn about cell division, they realized that there were other phases in the cell cycle; because they did not understand what was occurring in the cell at these times, the phases were called "G" (G_1 and G_2) for "gap." G_1 follows mitosis, and protein synthesis and RNA transcription are occurring during this phase. G_1 is extremely variable in length, depending on the cell type, ranging from 7 to 170 hours. G_2 precedes the next mitotic event and is usually brief, ranging from 1 to 4 hours. G_0 has been used to describe those cells that are not actively cycling. Certain cell types, such as myocytes and neurons, enter G_0 and rarely or never cycle again. Other cell types, such as hepatocytes, proliferate in young animals and then cease cycling at maturity but are capable of beginning to cycle again if cell replacement is necessary.

Table 18–1. Tumor Depopulation Related to Successive Drug Cycles Assuming a 90% Fractional Cell Kill in a Model System

Drug Treatment No.	Disease	No. of Tumor Cells	No. of Tumor Cells Surviving
1	Clinical	10,000,000,000 (10^{10})	1,000,000,000
2		1,000,000,000 (10^9)	100,000,000
	Complete clinical remission		
3	Subclinical	100,000,000 (10^8)	10,000,000
4		10,000,000 (10^7)	1,000,000
5		1,000,000 (10^6)	100,000
6		100,000 (10^5)	10,000
7		10,000 (10^4)	1,000
8		1,000 (10^3)	100
9		100 (10^2)	10
10		10 (10^1)	1
11		1 (10^0)	0

Chemotherapeutic drugs can be classified into three groups based on their activity in the phases of the cell cycle. Agents that are considered to be lethal to cells in all phases of the cell cycle, with resting cells as sensitive as proliferating cells, are called *cycle nonspecific*. Examples include nitrogen mustard and high-dose cyclophosphamide. Agents that are capable of damaging both resting and cycling cells (although cells in cycle are much more sensitive) include conventional-dose cyclophosphamide and doxorubicin. These drugs spare resting cells and are called *cycle specific*. Agents that are *phase specific* exert their lethal effects exclusively or primarily during one phase of the cell cycle, usually S or M; resting cells and cells in the other phases of the cell cycle are not killed. Examples include methotrexate, cytosine arabinoside, and vincristine.

Most cancers in animals as well as in humans are diagnosed only after they are well advanced. In the 1960s, Skipper used the rodent L1210 leukemia to illustrate this point and to determine cell kill kinetics in tumors (Skipper et al., 1964). The L1210 leukemia is a rapidly growing tumor with a growth fraction of 100% and a doubling time of only 12 hours. At this rate of growth, a billion cells would accumulate in the rodent only 19 days after injection of a single cell! After treatment of the leukemia with chemotherapy, Skipper et al. (1964) determined that cytotoxic drugs kill by log kill kinetics; that is, a given dose of an effective drug kills a constant fraction of cells and not a constant number, regardless of the number of cells present. This principle is known as the *fractional kill hypothesis*. For example, if a certain drug is known to kill 90% of the tumor cells present, it will kill 90% of the cells whether the beginning number is 10 cells or 10 billion cells. Thus, theoretically, it should be possible to cure with chemotherapy with rapid successive administration of chemotherapy drugs (Table 18–1). In fact, antineoplastic drugs kill an extremely variable fraction of cells, ranging from a very small fraction to a maximum of 99.99%; for many tumors, the fractional kill is disappointingly small. Theoretical "cures" with chemotherapy are prevented by (1) our inability to give drugs in rapid succession because of host toxicity and (2) the development of a drug-resistant population of tumor cells during the course of treatment.

Tumors as small as 1 g (10^9 tumor cells—1 billion) *may* be detected in the body, especially if they are located in areas like the skin or mouth. It is far more common, however, for tumors to escape detection until they are 10 g (10^{10} tumor cells) or more. The maximum malignant tumor mass compatible with life in humans is about 1 kg (10^{12} tumor cells). If one assumes that a given tumor originates from a single cell, then a 1-g tumor (10^9 cells) has gone through 30 doublings from the original cell. To get to 1 kg, only about 10 more doublings must take place. It should be clear from these sobering numbers that a large, unresectable tumor burden with only modest sensitivity to chemotherapy cannot be cured or, in many cases, even palliated with conventional chemotherapy administration protocols. The average volume doubling time for various human solid (i.e., nonleukemic) tumors is about 2 months. For certain rapidly growing tumors such as embryonal nephroma, seminoma, lymphoma, and the leukemias, however, the volume-doubling time is less than 1 month. For other tumors, the volume-doubling time is as long as 1 year. Because chemotherapy affects rapidly dividing cells, tumors with short volume-doubling times are generally chemotherapy sensitive, whereas tumors with long volume-doubling times are generally chemotherapy resistant.

In considering the efficacy of chemotherapeutic drugs, criteria have been described for measuring response. This evaluation is conventionally made after two cycles of chemotherapy have been administered:

Complete response (CR)—resolution of all measurable neoplastic disease for a period of at least 1 month. A chemotherapeutic drug that can cause a CR in a significant number of animals with a specific cancer is quite likely to increase disease-free survival, especially when used as an adjuvant agent.

Partial response (PR)—reduction in measurable tumor dimensions of at least 50% for at least 1 month. Although a temporary PR may provide the animal with some decrease in discomfort from the cancer, it is unlikely to have a significant effect on survival.

Stable disease (SD)—No change is noted in measurable tumor dimensions, or a response is seen that is less than a PR.

Certain criteria may be useful for declaring a treatment protocol ineffective or unsafe in a specific patient. Progressive growth (greater than 25%) in a measurable tumor lesion or the appearance of new lesions after two cycles of chemotherapy would suggest that the protocol is not useful for the tumor being treated. Severe toxicity with irreversible, cumulative, or unpredictable manifestations also generally suggests that the drug should no longer be used for this particular patient. If symptoms from the cancer lead to the patient's deterioration, with the only response to drug treatment being SD or PR, the drug should be discontinued and another treatment selected if possible.

The common cancers in dogs and cats can be broadly divided into three categories. The first category is *tumors in which the cells are exquisitely sensitive to chemotherapy.* In these tumors, CR can usually be obtained, and chemotherapy is therefore the accepted treatment of choice. Cure or complete, long-term remission can be expected, and surgery or radiation therapy will not generally be necessary to decrease cell numbers before chemotherapy is administered. An example would be the transmissible venereal tumor, for which an extremely high cure rate is possible with vincristine administration even when metastatic disease is present. Another example is lymphoma, for which rapid and complete response is seen with chemotherapeutic treatment. In most cases of lymphoma, however, remission lasts only 10 to 12 months because a drug-resistant population of tumor cells develops during treatment. For this reason, chemotherapeutic treatment of canine and feline lymphoma is generally considered to be palliative, not curative.

The second category is *tumors in which the cells are only modestly sensitive to chemotherapy.* Partial response may be obtained in some of these tumors, whereas in others response to drug treatment may be minimal. Chemotherapy may play a part in the management of these cancers but only with previous or concurrent surgery or radiation therapy. An example of this type of tumor is canine osteosarcoma, for which carboplatin is often used as an adjuvant treatment after amputation. *Adjuvant chemotherapy* is given along with or after another treatment modality, like surgery or radiation therapy, to increase the percentage of curative resections; in other words, it is used in hopes of converting a palliative treatment to a cure. Realistically, cures may occur but are rare in tumors with modest sensitivity to chemotherapy; palliation with some prolongation of life is generally the best result that can be expected.

The third category is *tumors for which chemotherapy is only rarely of any value for palliation or cure.* Progression of the cancer despite chemotherapeutic treatment is the outcome for most of these cancers. Many if not most tumors of dogs and cats fall into this category.

In principle, all cells that are actively cycling in the body should be sensitive to chemotherapy; however, the fact that chemotherapy is generally only modestly effective speaks to the fact that this is not entirely true. In many cancers, the tumor cells are actually less sensitive to cytotoxic drugs than are the hematopoietic cells within the marrow cavity. This forces a clinician to give a chemotherapeutic drug and wait to evaluate the toxic effects produced before another course of treatment can be administered. During the interval of time in which the dog or cat's neutrophil or platelet count is too low to receive another drug, endogenous hematopoietic growth factors are being produced, mediating proliferation of stem cells, and the bone marrow recovers and peripheral cell counts return to normal. Return of blood counts to normal after chemotherapy is the usual point at which another course of treatment may be given. It is important not to give another cycle of chemotherapy when peripheral blood counts are extremely low because stem cells are actively proliferating at this time; treatment with cytotoxic drugs administered when stem cells are actively dividing increases the chance that the stem cell population may be killed and recovery may never occur. In humans this is the point at which bone marrow or stem cell transplantation is performed.

Unfortunately, tumor cells may recover from chemotherapeutic injury and begin to proliferate again before the animal's marrow recovers. Even when a tumor is exquisitely sensitive to drug treatment and an apparent complete response is obtained, a line of drug-resistant cells often develops. It is a common clinical experience to find that a tumor may respond quite well to the first treatment with a drug, with progressively less impressive responses as the drug is given repeatedly. Classically, multiple-drug resistance occurs when large numbers of the cells in a tumor express a gene that produces P-glycoprotein, a transmembrane protein important in cell transport. This protein pumps chemotherapeutic drugs from the inside of the cell to the extracellular environment so that they cannot act within the cell. Other mechanisms leading to acquired drug resistance include (1) the development in the tumor cell of alternate metabolic pathways to avoid the chemotherapeutic drug's mechanism of action; (2) a decrease in the fraction of tumor cells actively dividing after several cycles of treatment, thus protecting the remaining cells against damage; and (3) tumor cells may enter a biologic "sanctuary site" in which they are protected from injury because of a lack of drug diffusion into that area (i.e., brain). Delaying administration of chemotherapy because of hematopoietic or gastrointestinal toxicity often results in a patient in apparent "remission," with no visible neoplastic disease but with large amounts of microscopic tumor.

Multiple-drug resistance ultimately develops as a result of chemotherapy being administered in a regimen that is "too little, too late." The highest possible doses of chemotherapy given as frequently as can be tolerated by the patient, early in the course of the neoplastic disease (when smaller numbers of cells are present), have a much higher chance of producing a cure than chemotherapy given after a large number of tumor cells have infiltrated various organs. In humans, the wait for marrow recovery has been overcome with the use of bone marrow or stem cell transplants, performed after chemotherapy treatment given in doses high enough to kill tumor cells as well as ablate normal marrow cells. The extreme expense, technical difficulty, and morbidity of this procedure do not allow for its use in dogs and cats as a routine clinical procedure as yet. In veterinary oncology in the waning days of the twentieth century, we are limited to palliation of tumors; only rarely can we expect to cure.

A regimen of chemotherapy treatment can be divided into several phases. The period of *induction* is the initial intensive chemotherapy intended to produce *remission.* Remission is defined as the point at which no measurable tumor mass can be found; for lymphoma, remission is declared when the enlarged lymph nodes, liver, and spleen have returned to normal size and malignant cells have disappeared from the bone marrow. This does not mean that all (or even most) tumor cells have been killed, however, and *consolidation* therapy with different drugs may be given after apparent clinical remission to produce a larger tumor cell kill. For some tumors such as lymphoma, the animal may be given "pulse" doses of drugs after induction and consolidation to maintain the gains obtained with the induction protocol; this is called the *maintenance* phase of chemotherapy. Recently, *intensification* protocols have been described for tumors in which drug resistance is common. These protocols are administered during the maintenance period when the patient is in apparent remission and are an attempt to kill developing drug-resistant clones of cells by using one or two drugs at high doses.

"Combination" chemotherapy is, in general, more effective than single-agent therapy. Use of multiple drugs sequentially provides additive antitumor effects without greatly increasing host toxicity, especially if drugs are selected carefully. Combination chemotherapy may delay tumor resistance to drugs compared with single agents. Picking different drugs that have effects on more than one cell-cycle phase may also result in a greater fractional cell kill per cycle of chemotherapy.

There are three phases in the development of a new chemotherapeutic drug. Many man-made chemicals and naturally occurring compounds are screened (generally by the National Cancer Institute or by industry) for cytotoxicity, first in cultures of cancer cells and then in mice or rats. If a particular compound looks promising, a *Phase I* trial is conducted, providing an initial pharmacologic evaluation. The appropriate mode of administration is established for the drug, and common side effects are discovered. Patient tolerance of increasing dosage is also determined. Phase I trials are conducted on very small numbers of patients, generally with advanced and ultimately terminal cancers for which no conventional treatment is available, and doses tolerated by these patients may be below the ultimate therapeutic range. If the compound shows no prohibitive toxicity and shows even slight efficacy (SD or PR in a few patients), the *Phase II* trial begins. In this phase, "screening" for efficacy of the drug against a variety of tumors is conducted. After the spectrum of activity is determined, dose-response relationships are determined. The *Phase III* trial is then used to determine drugs that work effectively together, and the new combination protocol is ultimately compared with the existing "best" treatment.

Traditionally, in estimating the appropriate dose of a drug to administer to a patient, clinicians have used body weight of the patient as the main criterion; the dose has been figured as the number of milligrams per kilogram to be given. In a series of studies begun in the 1880s, however, it was demonstrated that many physiologic parameters could better be estimated on the basis of body surface area (BSA). Basal metabolic rate, blood volume, cardiac output, and renal function parameters were found to correlate much better with the individual's BSA than with weight. It was then found that drug doses calculated per unit of body weight were greater in smaller animals and children than in larger animals and adults, whereas doses calculated per unit of surface area were similar for all species and ages. Based on the findings in these studies, researchers concluded that BSA might be useful as a standard for calculating drug doses in cancer chemotherapy. The calculation for determining BSA for a given species is made by using the formula

$$\text{BSA in m}^2 = \frac{K_m \times W^{2/3}}{10^4}$$

In the above formula, K_m is a factor based on the different metabolic rate of each species; for the cat it is 10.0, and for the dog it is 10.1. W is the body weight in grams. Because the K values for dogs and cat are quite close, a table has been formulated that allows for quick estimation of the BSA based on the animal's weight in kilograms (Table 18–2). The appropriate dose of the chemotherapeutic agent to be administered is calculated by multiplying the dose/m² by the patient's BSA (m²) taken from the table. A serious and potentially fatal mistake made by some clinicians when using a nomogram or table to estimate the BSA has been to use the animal's weight in *pounds* rather than in kilograms. To avoid this, a good rule is to calculate the dose of a chemotherapeutic drug yourself and then ask another individual to separately calculate it also before the drug's administration.

Recently, the use of BSA as a means of calculating doses for all chemotherapeutic agents has been questioned. For many chemotherapy drugs, myelosuppression is the most common form of toxicity and is dose limiting; it has been found that BSA does not correlate well with either stem cell number in the bone marrow or resulting hemato-

Table 18–2. Conversion Table of Weight to Body Surface Area in Meters for Dogs

Kg	M^2	Kg	M^2
0.5	0.06	26.0	0.88
1.0	0.10	27.0	0.90
2.0	0.15	28.0	0.92
3.0	0.20	29.0	0.94
4.0	0.25	30.0	0.96
5.0	0.29	31.0	0.99
6.0	0.33	32.0	1.01
7.0	0.36	33.0	1.03
8.0	0.40	34.0	1.05
9.0	0.43	35.0	1.07
10.0	0.46	36.0	1.09
11.0	0.49	37.0	1.11
12.0	0.52	38.0	1.13
13.0	0.55	39.0	1.15
14.0	0.58	40.0	1.17
15.0	0.60	41.0	1.19
16.0	0.63	42.0	1.21
17.0	0.66	43.0	1.23
18.0	0.69	44.0	1.25
19.0	0.71	45.0	1.26
20.0	0.74	46.0	1.28
21.0	0.76	47.0	1.30
22.0	0.78	48.0	1.32
23.0	0.81	49.0	1.34
24.0	0.83	50.0	1.36
25.0	0.85		

poietic toxicity. In fact, correlation is highly significant between bone marrow effects of the cytotoxic drugs and body weight.

A Phase I study in dogs was performed to evaluate toxicity of doses of intravenous melphalan calculated by BSA. A significantly greater number of small dogs experienced significant toxicity than did large dogs (Page et al., 1988). Another study compared marrow toxicity induced by doxorubicin given at 30 mg/m^2 to that induced by the drug given at doses calculated at 1 mg/kg (Arrington et al., 1994). It was found that a disproportionately greater number of dogs weighing less than 10 kg developed severe myelosuppression at the 30 mg/m^2 dose than at the 1 mg/kg dose. Limited toxicosis was seen in dogs weighing greater than 10 kg with either of the dosing schemes, however. Plasma doxorubicin concentrations were less after treatment at the 1 mg/kg dose in both large and small dogs than in those given 30 mg/m^2, and it is possible that 1 mg/kg may be an inappropriately low dose for treatment of animals with cancer.

For drugs that may produce severe myelosuppression, measurement of hematopoietic stem cell numbers for each individual patient would clearly provide the most information to prospectively calculate doses for chemotherapeutic agents. Until such a test is available, however, we must use the doses available in the literature, always carefully taking into account the individual animal's response to the previous drug dose before administering the next treatment. If a dose of 1 mg/kg is well tolerated by a dog or cat weighing less than 10 kg, the next dose may be increased slightly, gradually approaching the dose calculated by BSA; this is called *dose escalation.*

In daily clinical practice, we judge the adequacy of therapy by measuring the response of visible, measurable masses; only much later are we able to evaluate the results of our treatment by survival results. In a rodent model for osteosarcoma, reduction in the dose intensity of melphalan and cyclophosphamide caused a marked decrease in the cure rate *long before there was a reduction in the rate of complete clinical remission.* On the average, it is estimated that a dose reduction of approximately 20% leads to a loss of 50% in the cure rate (DeVita, 1993). A positive relationship between dose intensity and response rate has been demonstrated in many human tumors, including lymphoma and ovarian, colon, and breast cancers. We should administer the highest dose of a chemotherapeutic drug that can be tolerated by the patient if we are attempting to cure; if palliation is our only goal, a dose that will produce clinical remission without dose escalation is possibly appropriate. Careful patient monitoring for therapeutic response and toxicity is still the best way to titrate the drug dose for each individual patient.

Because chemotherapeutic drugs are quite toxic, the following guidelines for making the decision to begin chemotherapy are critically important:

1. Use chemotherapeutic agents only when a diagnosis of malignancy has been established definitively, either by cytology or histopathology.
2. Determine whether the particular tumor is known to respond to the treatment in a reasonable percentage of cases, with toxicities that will be tolerated by the patient and its owner.
3. Follow objective measurements of the tumor or its markers (e.g., hyperglobulinemia, hypercalcemia) if at all possible to determine whether the chemotherapy being administered is of benefit or should be discontinued.
4. Do not use chemotherapy for a patient unless proper supportive facilities are available for monitoring and treatment of any complications.
5. Do not use chemotherapy unless the animal's owner is likely to be compliant with instructions for drug administration and monitoring and observant of early signs of complications.

COMMON SIDE EFFECTS OF CHEMOTHERAPY

Cells of normal tissue are damaged by chemotherapy; most, given time, will recover. Tissues that are especially affected include those in which the cells have a short life span and require constant renewal (i.e., bone marrow, gastrointestinal mucosa, gonads, and hair follicles). Myelosuppression and subsequent infection are the most common dose-limiting toxic effects of chemotherapy. Drugs that seem to be particularly myelosuppressive in dogs and cats include cyclophosphamide, carboplatin, doxorubicin (particularly when used in combination with another chemotherapeutic agent), CCNU (chloroethyl-cyclohexyl-nitrosourea), BCNU (bischloroethyl-nitrosourea), and vinblastine. In some cats, vincristine has been noted to produce a marked and prolonged neutropenia (Hahn et al., 1996).

Many mechanisms contribute to infection after chemotherapy. Certain chemotherapeutic agents prevent phagocyte mobilization or impair function of these cells. Some cancers infiltrate the bone marrow, producing myelophthisis and contributing to cytopenias. Suppression of leukopoiesis by chemotherapy drugs may lead to associated barrier disruptions of the skin, oral cavity, and alimentary tract mucus, and the normal pulmonary "mucociliary elevator" may not function effectively to clear bacterial organisms. Endogenous bacterial infections may develop, caused by the host's native microbial flora; these are commonly due to aerobic and anaerobic gram-negative rods from the gastrointestinal tract or *Staphylococcus* from the skin. In addition, hospitalized patients frequently develop catheter-related bacteremias, often due to microbes transmitted to the susceptible patient from the hospital environment or from another animal; these organisms may be antibiotic resistant.

Patients with absolute neutrophil numbers more than 1500/μL are generally protected against endogenous infections. From 1000 to 1500/μL, the owner is advised to monitor the animal's condition and report any fever or anorexia. From 500 to 1000/μL, prophylactic antibiotics are generally dispensed unless the period of neutropenia is anticipated to be very short. When the absolute neutrophil number is less than 500/μL, the animal should probably be hospitalized for intravenous antibiotic administration, and treatment with granulocyte colony-stimulating factor may be considered. In general, antibiotics should not be given prophylactically for neutropenia unless necessary because they increase risks for development of bacterial resistance and for fungal infection in the immunocompromised patient.

When necessary, choice of an empirical antibiotic regimen should take into account the type of infection the patient is likely to have—home acquired (probably endogenous) or hospital acquired (likely to be exogenous and possibly antibiotic resistant). An appropriate antibiotic combination for use in the febrile neutropenic patient is an aminoglycoside plus an antipseudomonal penicillin (ticarcillin, carbenicillin, piperacillin) or cephalosporin (cephalothin, cefazolin, cefoxitin). The third-generation cephalosporin ceftazidime is an antibiotic with an excellent spectrum of efficacy against gram-negative bacteria and *Pseudomonas*, and it is moderately effective for treatment of *Staphylococcus* infections. Because it has poor efficacy against anaerobic organisms, it must be combined with a drug like clindamycin or metronidazole or an antipseudomonal penicillin; these combinations are very useful to treat infections in neutropenic cancer patients. Imipenem is useful as a single agent for these patients, with excellent efficacy against enteric gram-negative bacteria, *Pseudomonas*, anaerobes, and *Staphylococcus*, but the high cost of this antibiotic usually prevents its use in veterinary medicine at this time.

If myelosuppression is severe and life threatening, recombinant granulocyte-colony stimulating factor (rhG-CSF) may be administered. This is a human glycoprotein that regulates production of neutrophils within the bone marrow and is produced in *Escherichia coli* bacteria. It stimulates neutrophil progenitor proliferation, differentiation, and functional activity with minimal toxicity. Long-term use of the human product in the dog or cat (longer than 30 days) resulted in antibody formation, however, with significant and prolonged decreases in neutrophil counts (Hammond et al., 1991). At a daily dose of 5 μg/kg subcutaneously, the effects of canine rG-CSF on the normal canine bone marrow are rapid and predictable (Obradovich et al., 1990): Mean neutrophil counts in normal dogs increased to 26,330/μL after one injection, with a maximum count of 72,125/μL by day 19 of administration. The neutrophil counts returned to normal in these dogs within 5 days after discontinuing daily therapy. Recombinant human G-CSF has resulted in similar elevations of neutrophil counts in the dog (Lorthrup et al., 1988). In cats, 10–14 days of rhG-CSF resulted in maximum neutrophil counts ranging from 20,370 to 61,400/μL (Fulton et al., 1991). Thus, a short course of rhG-CSF may be used in dogs or cats either *before* aggressive chemotherapy in an attempt to ameliorate or prevent myelosuppression or as a rescue *after* chemotherapy has induced significant neutropenia.

Another frequent side effect of chemotherapy relates to the gastrointestinal toxicity of these drugs; anorexia, vomiting, and diarrhea may be noted in some individuals treated with cytotoxic agents. These side effects are not noted in the dog and cat as predictably as in humans, but can occur in sensitive individuals with most of the commonly used drugs. Agents with a high potential for acute nausea after administration include cisplatin, dacarbazine, the nitrosoureas, and high-dose cyclophosphamide; those with a moderate potential include carboplatin, conventional-dose cyclophosphamide, doxorubicin, mitoxantrone, and, occasionally, vincristine. In animals with only mild to moderate nausea, metoclopramide or prochlorperazine may be effective. Premedicating with subcutaneous administration of butorphanol at 0.4 mg/kg often blocks the postadministration vomiting caused by cisplatin administration (Moore et al., 1994a).

In animals with severe nausea and vomiting from chemotherapy (which is, luckily, rare), the serotonin 5-hydroxytryptamine (5-HT) receptor antagonists may be given either orally, subcutaneously, intramuscularly, or rectally. The most commonly available member of this class of drugs is ondansetron, but several newer antiemetics of the class are under development or are in clinical trials in humans; they are currently very expensive. The dose of ondansetron for the dog is 0.1 to 0.2 mg/lb subcutaneously two to three times daily. The serotonin receptor antagonists act more specifically than other antiemetics to prevent the vomiting induced by chemotherapy or radiation. Serotonin receptors of the 5-HT type are located on vagus nerve terminals and in the chemoreceptor trigger zone. Serotonin is released from enterchromaffin cells in the small intestine when they are severely damaged. The released serotonin stimulates vagal afferents through the 5-HT receptors, and nausea and vomiting ensue. Ondansetron blocks the 5-HT receptor site, which prevents the serotonin effect.

Other gastrointestinal side effects may also occur. Doxorubicin sometimes produces a severe hemorrhagic colitis in dogs, for which hospitalization and symptomatic treatment with antibiotics and intravenous fluids may be necessary. Anorexia may be noted with several drugs, especially in cats with doxorubicin or vincristine administration. Appetite stimulation with cyproheptadine may help these cats, but enteral feeding is occasionally necessary.

Several commonly used chemotherapeutic drugs produce phlebitis, local necrosis, or both at the site of administration if extravasated. Those that can be expected to produce severe reactions include the vinca alkaloids, doxorubicin, and dactinomycin; moderate reactions may be seen with 5-fluorouracil, bleomycin, cisplatin, dacarbazine, and mitoxantrone. These cytotoxic drugs may irritate the lining of access veins during administration, producing phlebitis, or may escape the cutaneous vasculature and spread throughout the surrounding tissues, causing a local inflammatory reaction (chemical cellulitis). Alternatively, some of the drugs produce local tissue necrosis when extravasated. With doxorubicin, the most dramatic and severe reactions are produced. Extravasation produces marked epidermal hyperplasia, with mitosis of many epidermal cells at the margins of the lesion; the reaction will contain individual necrotic keratinocytes, lobular panniculitis, and reactive fibroblasts and endothelial cells. No inflammatory reaction will be seen. In the area of direct extravasation, panepidermal, dermal, and subcutaneous tissue necrosis will be present. This necrosis begins 1 to 2 weeks after the drug is extravasated and may continue for up to 4 months.

With all these drugs, extreme precautions should be taken to prevent extravasation, with meticulous care with venipuncture and catheter placement. The infusion should be terminated immediately if the patient shows signs of pain during drug administration. If the catheter or needle is still present, aspirate any fluid possible from the extravasated area. For vinca alkaloid extravasation, inject 150 U of hyaluronidase through the patent catheter or needle and apply local heat for 15 to 30 minutes four times a day for 48 hours. For anthracycline extravasation, apply an ice pack for 15 to 30 minutes four times a day and 90% DMSO topically several times daily for 72 hours; consider surgical removal if the area of extravasation is confined. Because treatment is not particularly effective in preventing the local irritation or necrosis caused by extravasation of these drugs, prevention is the best answer!

Alopecia is common in certain breeds of dogs after chemotherapy, particularly after administration of doxorubicin or cyclophosphamide. Hair loss is predictable in poodles and in mixed-breed dogs of poodle lineage; it is also seen commonly in terriers and Old English sheepdogs. Occasionally, it may be noted in other breeds as well. It is common for cats to lose their whiskers during chemotherapy. For some owners, the alopecia induced by chemotherapy is very distressing, and owners of breeds in which this is likely to occur should be prepared for this possibility. Hair regrowth begins within 1 to 2 months after chemotherapy is discontinued. An alteration in the color or texture of the new hair may, however, be noted; the regrown hair may be a lighter or darker shade and may be softer or curlier than the animal's "normal" hair.

Although generally less important for dogs and cats with cancer than for humans, the effects of chemotherapy on gonadal function should be explained to owners considering treatment, particularly if the animal is shown or has been used for breeding. Most of the drugs discussed in this chapter cause hypofertility or infertility by impairing production of sperm and oocytes. Loss of libido may result in the male due to Leydig cell dysfunction and decreased testosterone levels, especially with corticosteroid treatment for lymphoma. Owners should consider cryostorage of sperm from the dog before chemotherapy is begun. It is common, however, to find on semen evaluation that general debility from the cancer itself has resulted in poor semen quality even before chemotherapy has been given. Reversibility of the gonadal dysfunction is variable depending on the chemotherapeutic agent used, the dose intensity of the protocol used for treatment, and the age of the patient itself. During chemotherapy and for a variable period after the treatment is completed, a male dog should not be used for breeding and a female should not become pregnant, as congenital malformations may result in the puppies.

Finally, exposure of hospital personnel and owners to carcinogenic, mutagenic, and teratogenic drugs and drug-containing animal waste must be considered. There have been many reports in the human literature of fetal loss and birth of infants with congenital defects to nurses and pharmacy staff members routinely exposed to chemotherapy drugs. Proper storage, preparation, and administration of chemotherapy drugs, as well as proper disposal of cytotoxic drug waste and urine and stool of the animal being treated, should be a concern of every clinician who treats an animal for cancer. Reviews on proper handling of chemotherapy in the workplace are available (Swanson, 1988a, b). Occupational Safety and Health Administration (OSHA) Guidelines for Cytotoxic (Antineoplastic Drugs), Publication 8–1.1, may be downloaded from the OSHA's website at http://www.osha-slc.gov:80/SLTC/hazardousmedications/index.html.

DRUGS USED IN CANCER CHEMOTHERAPY

The drugs discussed are commonly used in veterinary oncology for the treatment of canine and feline neoplasia. Included are selected cautionary comments about administration, toxicity, and effectiveness. Because dosages for chemotherapy drugs vary greatly depending on tumor type and protocol used, no table of drug doses is provided in this chapter. It is extremely important that a clinician considering the use of one of these drugs as a single agent or in a combination protocol carefully consider all of the drug's possible toxicities rather than just look up a dose from a chart or formulary.

Alkylating Agents

Cyclophosphamide

Mechanism of Action Cyclophosphamide is a classic alkylating agent that is extensively metabolized in the liver to the active cytotoxic metabolites phosphoramide mustard and acrolein. The metabolite phosphoramide mustard is responsible for most of the antineoplastic effects of the drug. Cyclophosphamide is cell cycle specific at normal dosing schedules but may be cell cycle nonspecific at extremely high doses. Resistance to treatment with cyclophosphamide does develop in tumor cells, probably related to increased ability of the tumor cells to produce glutathione and obtain protection from oxidative damage. Excretion takes place principally by the kidneys, and modification of dose and dose interval should be considered when a patient has significant renal disease.

Preparations Cyclophosphamide is available as 25-mg and 50-mg tablets for oral administration and as an intravenous preparation in vials containing 100 mg, 200 mg, or 500 mg. The drug is equally effective when given orally or parenterally. Cyclophosphamide cannot be used for intracavitary treatment because it must be metabolized to its active form in the liver.

Side Effects Cyclophosphamide has the potential to cause extremely dangerous marrow suppression as well as nausea and vomiting. Of all the chemotherapeutic drugs in common use in veterinary oncology, neutropenia occurs most predictably with cyclophosphamide. As a result, the drug must initially be cautiously administered; the degree of myelosuppression varies from patient to patient but may be early and profound. For this reason, neutrophil counts must be carefully assessed whenever the drug is used for the first time in a patient. Some animals will develop myelosuppression from 1 week of cyclophosphamide; in others, the drug will have to be discontinued after 3 to 5 days due to severe neutropenia, thrombocytopenia, or both.

A baseline total white blood cell count, differential, and platelet estimate should be obtained before the drug is administered. Usually, depression in the absolute neutrophil count begins on the third day of administration, so the next blood count is taken on that day. From that day on during the first cycle of cyclophosphamide therapy, a total leukocyte count, differential, and platelet estimate are obtained every day until the cycle of cyclophosphamide therapy is completed. If the absolute neutrophil count drops below 3000/μL, the drug is discontinued entirely for that cycle; on the next cycle, it is reinstituted at a dose 25% less than the initial daily dose. If the neutrophil count drops to less than 1500/μL, the drug is stopped and reinstituted on the next cycle at a dose 50% less than the initial dose. If the number of neutrophils drops to less than 1000/μL and fever ensues, empirical antibiotic therapy should be begun. Recombinant human G-CSF may also be given for several days if necessary until the animal's neutrophil count returns to normal. After the animal's individual tolerance for cyclophosphamide is determined, fewer complete blood count will need to be checked during therapy. In maintenance protocols, one complete blood count per cycle before administration of the drug is begun is generally adequate.

Hemorrhagic cystitis may occur due to cyclophosphamide administration, usually after long-term use; however, it has been reported after one intravenous administration (Peterson et al., 1992). It is caused by the metabolite acrolein, which is excreted in urine and reaches a urine level of 100 to 200 times the serum concentration; this metabolite is extremely irritating to the bladder mucosa and produces necrosis of smooth muscle. Chronic cystitis leading to bladder fibrosis may occur with long-term use. Affected dogs and cats will present with clinical signs of gross hematuria, often with blood clots, and will be reported to be straining to urinate. Concurrent treatment with prednisone decreases the incidence of hemorrhagic cystitis, probably by causing polydipsia and polyuria. Lymphoma patients rarely develop this complication because prednisone administration is generally a part of the treatment protocol.

Any animal that is to receive cyclophosphamide should have a urinalysis performed before the drug's administration to rule out pre-existing hematuria due to bacterial cystitis or prostatitis. The client should be warned to watch for hematuria during the course of treatment with cyclophosphamide, and administration should cease immediately if the problem is noted. Several precautions can help to avoid this problem while an animal is receiving cyclophosphamide. The animal should be encouraged to drink more fluids; salting food and offering beef or chicken bouillon may help to increase fluid intake. Because the cystitis is caused by acrolein producing local irritation on the bladder mucosa, the owner should encourage frequent urination by walking his or her dog more frequently and should make sure that the dog is allowed to urinate before retiring for the night. It is better not to administer cyclophosphamide in the evening, as acrolein will then concentrate in the urine overnight. Although the free-radical scavengers acetylcysteine and mesna have been reported to prevent cyclophosphamide-induced hemorrhagic cystitis in humans treated with high-dose cyclophosphamide before bone marrow transplantation, it is not clear that they are necessary for dogs and cats treated with standard chemotherapy protocols. The incidence of this side effect seems to be low with most current cyclophosphamide dosing regimens, which use intermittent "pulse" doses of cyclophosphamide rather than continuous daily dosing of the drug.

Alopecia occurs in susceptible dogs as another side effect of cyclophosphamide. When cyclophosphamide is used in combination with doxorubicin or dactinomycin, cardiotoxicity of these compounds may be potentiated.

Dosing Regimen Cyclophosphamide is usually given in doses from 50 to 100 mg/m² daily orally for 4 to 7 days per week according to the particular tumor protocol. It may also be given intravenously at 200 mg/m² once weekly, but this protocol is likely to be dangerously myelosuppressive for some dogs.

Melphalan (Phenylalanine Mustard)

Mechanism of Action Melphalan is an alkylating agent that is a phenylalanine derivative of mechlorethamine, the first chemotherapeutic agent discovered. In World War I, it was noted that troops who had received poisoning with mustard gas often had aplastic anemia and severe lymphopenia, with depletion of lymphocytes in the spleen and lymph nodes. This finding caused clinicians to study the effects of nitrogen mustard on lymphoma, first in the mouse and later in humans. Many derivatives of this original compound have been discovered, but melphalan remains one of the most useful.

Spectrum of Activity In dogs and cats, melphalan is generally used for the treatment of plasma cell tumors, either plasma cell myeloma or extramedullary plasmacytoma (Trevor et al., 1993).

Preparations Melphalan is available for oral use as a scored 2-mg tablet and for intravenous injection as a 50-mg vial. In dogs and cats, the drug is conventionally used orally.

Side Effects Myelosuppression is the most common side effect of melphalan, but it is not generally severe. Monitoring of a complete blood count should be done every 2 weeks during induction and then monthly during maintenance.

Dosing Regimen The recommended dose for melphalan is 0.1 mg/kg for 7 to 10 days and then 0.05 mg/kg per day until remission is achieved. The drug is then given as a maintenance agent for 7 days out of every month at 0.1 mg/kg per day. Because food can apparently decrease the oral absorption of the drug, it should be given several hours before the animal is fed.

Chlorambucil

Mechanism of Action Chlorambucil is another derivative of nitrogen mustard; it is the slowest acting and least toxic of the alkylating agents commonly used in veterinary medicine. The drug is easily absorbed by passive diffusion when administered orally, so food given with it may interfere with its absorption.

Spectrum of Activity Chlorambucil is used as a mainstay for treatment of chronic lymphoctyic leukemia (MacEwen et al., 1977), small cell lymphoma, Waldenstrom's macroglobulinemia, and thymoma in dogs and cats. It has been substituted in combination chemotherapy protocols for cyclophosphamide when hemorrhagic cystitis has ensued, but it is not especially effective for maintenance therapy of high-grade lymphomas. Activity may also be seen against plasma cell myeloma and ovarian carcinoma.

Preparations Chlorambucil is available as a 2-mg tablet for oral administration only.

Side Effects Marrow suppression is quite late, gradual in onset, and rapidly reversible in dogs and cats, but it may be profound if it is not discovered early enough. In general, myelosuppression is not seen until the drug has been given daily for at least 1 month; it is recommended that a complete blood count be obtained once every 2 weeks during induction. As soon as remission occurs, the drug should be administered only intermittently as a maintenance protocol (i.e., alternate weeks or 1 week out of 4). Chlorambucil should not be administered with food.

Dosing Regimen The dose for chlorambucil is 0.1 to 0.2 mg/kg orally daily for 4 to 7 days and then 0.1 mg/kg daily until remission occurs. Alternatively, the drug may be given once every 2 weeks at a dose of 0.4 mg/kg. After remission is obtained, a maintenance protocol may be started, with the drug administered intermittently as indicated by the tumor treated, that is, 0.1 mg/kg daily for 7 consecutive days a week followed by 21 days off.

Nitrosoureas

Mechanism of Action CCNU (lomustine) and BCNU (carmustine) are drugs that are very lipid soluble and cross the blood-brain barrier with ease. Excretion is primarily renal, so dose modification must be considered if the patient has renal disease.

Spectrum of Activity Although CCNU and BCNU are used in humans to treat certain lymphomas, the drugs find their principal use in veterinary medicine for treatment of central nervous system neoplasia (Dimski and Cook, 1990; Fulton and Steinberg, 1990); the two drugs are unique in their ability to attain therapeutic levels in brain tissue. Recent information suggests that CCNU may also have some efficacy in treatment of canine mast cell tumor.

Preparations BCNU is available in a 100-mg vial for intravenous administration. CCNU is given orally and is available as 10-, 40-, and 100-mg capsules.

Side Effects Both of the nitrosoureas may be quite emetogenic immediately after administration. The vomiting and nausea usually last less than 24 hours after administration and the animal's discomfort can generally be ameliorated with butorphanol given subcutaneously at 0.4 mg/kg three times a day. In some cases, ondansetron will be necessary to relieve symptoms.

Prolonged bone marrow suppression is common with both of the nitrosoureas. Neutropenia may be noted as early as 1 week after administration but may persist for up to 6 weeks. In some cases, neutropenia is severe enough to adversely affect the animal's quality of life, and treatment with intravenous antibiotics and rhG-CSF may be necessary if the animal becomes febrile.

Dosing Regimen BCNU must be given intravenously. The product is reconstituted with alcohol and then added to saline or 5% dextrose in water to be given as an intravenous (IV) infusion over 1 to 2 hours. Severe pain may occur at the injection site even if no extravasation is seen; a longer infusion time may help to decrease discomfort from the administration. The conventional dose of BCNU is 50 mg/m^2 given intravenously once every 6 weeks. CCNU is available as an oral preparation, and it is given as a single oral dose of 60 to 75 mg/m^2 once every 4 to 6 weeks.

Dacarbazine

Mechanism of Action The major mode of action of dacarbazine (DTIC) against tumor cells appears to be alkylation of nucleic acids. Its complete chemical name is 5-(3,3-dimethyl-1-triazeno)-imidazole-4-carboxamide, hence the name DTIC. Dacarbazine is cycle specific.

Spectrum of Activity Dacarbazine is not often used in veterinary oncology. At one time, it was suggested as treatment for canine melanosarcoma, but results were disappointing. Dacarbazine has its major use for treatment of relapsed lymphoma in combination with doxorubicin (Van Vechten et al., 1990).

Preparations Dacarbazine is available for IV administration in vials of 100, 200, and 500 mg.

Side Effects Local pain is often seen during administration; concentrated solutions of the drug are very irritating to veins, and extravasation will produce severe phlebitis. Myelosuppression is mild and does not occur until the second or third week after treatment, but a complete blood count should be checked before administration of each subsequent treatment. Vomiting and nausea are common during the first few days of treatment but can usually be blocked by prior administration of chemoreceptor trigger zone-blocking antiemetics. These gastrointestinal symptoms may be lessened by a lower dose initially and gradual escalation of the dose during the course of treatment, but the signs seem to subside after 1 or 2 days of treatment despite continued therapy with DITC.

Dosing Regimen Dosage is 150 to 250 mg/m^2 given slowly intravenously for 5 days. Treatment is repeated every 3 weeks.

Mitotic Inhibitors: Vinca Alkaloids

Mechanism of Action The vinca alkaloids are extracted from the common periwinkle plant, *Vinca rosea.* This plant was originally investigated by pharmacologists because of its reported ability to lower blood glucose levels in several native populations. Although its efficacy as a hypoglycemic agent was found to be unimpressive, it was discovered that extracts of the plant had cytotoxic effects. Eventually, vincristine and vinblastine came into common clinical use as anticancer agents; the two compounds differ only slightly, with vincristine having a formyl side chain and vinblastine having a methyl side chain on the larger parent molecule. Both of the drugs appear to act as spindle poisons by binding to microtubular proteins within cells.

The spindles are thus unable to act during mitosis, leading to arrest of the cell in metaphase. Generally, vincristine is thought of as a phase-specific drug effective only in the M phase of the cell cycle. Vinblastine, however, also blocks the cell's utilization of glutamic acid, thus inhibiting purine synthesis. For this reason, vinblastine acts against cells in active mitosis but also in other phases of the cell cycle.

Spectrum of Activity Vincristine and vinblastine have their major use in veterinary medicine in combination chemotherapy protocols for treatment of lymphoma and lymphoid leukemias. Some efficacy of vincristine may be seen either as a single agent (Hahn, 1990) or in combination with doxorubicin and cyclophosphamide for treatment of soft tissue sarcomas (Hammer et al., 1991), and vincristine is the drug of choice for treatment of transmissible venereal tumor (Calvert et al., 1982; Singh et al., 1996). Although it was previously suggested that vincristine might be effective in the treatment of mast cell tumor in the dog, a recent report has discounted the drug's role in management of this tumor, only 2 of 27 dogs with mast cell tumors had even a partial response to vincristine given at 0.75 mg/m^2 (McCaw et al., 1997). The principal use of vinblastine in veterinary oncology at this time is as a substitute for vincristine in a combination chemotherapy protocol when a vincristine-induced neuropathy has been noted.

Preparations Vincristine is available for intravenous use in 1-, 2-, and 5-mg vials. Vinblastine is also for IV administration only, and is supplied in 10-mg vials.

Side Effects Because of its phase-specific effects, vincristine is not generally myelosuppressive in the dog; occasionally, it may produce significant neutropenia in the cat (Hahn et al., 1996). Anorexia and nausea are sometimes seen in both dogs and cats treated with vincristine, especially at the higher levels of the dose range. Unlike vincristine, vinblastine is quite myelosuppressive, and the interval between doses is often prolonged because of the duration of neutropenia produced by the drug.

Local phlebitis and severe pain occur if either of the vincas is extravasated. Although a catheter may be placed, conventionally a butterfly needle is used to administer vincristine or vinblastine. The vein is punctured with the butterfly needle in the usual fashion, and blood flow is observed into the tubing. Several milliliters of saline are infused into the vein to observe for leakage. The vinca alkaloid is then given as a bolus injection and is followed by several more milliliters of sterile saline to make sure that not a drop of the drug remains on the tip of the needle.

One of the principal limitations of long-term treatment with vincristine in clinical practice is the development of a drug-induced sensory and motor neuropathy, the pathogenesis of which is poorly understood. The cat may be more sensitive to the development of this phenomenon than the dog (Todd et al., 1979). Severe nerve fiber degeneration may be seen, as well as focal axonal swellings with secondary demyelination of peripheral nerves (Cho et al., 1983; Hamilton et al., 1991a). Vincristine administration should be discontinued immediately as soon as any signs of neuropathy are noted, because further treatment may produce severe, generalized motor weakness. The neurotoxicity will generally improve within several months after the drug is discontinued, but some of the signs may be irreversible. Although neurologic problems are rare with vinblastine administration, they may rarely occur with this drug as well.

Dosing Regimen The appropriate dose of vincristine is 0.5 to 0.75 mg/m^2 intravenously once weekly according to the treatment protocol used. Treatment with vinblastine should begin at 2 mg/m^2 by IV injection once every 2 weeks. At each cycle, increase the vinblastine dose in increments of 0.25 mg/m^2 until myelosuppression is seen (absolute neutrophil count less than 3000/μL). Then, give a maintenance dose of vinblastine that is *one increment smaller than the dose that produced leukopenia.* Because vinblastine is very myelosuppressive, do not administer the drug when an animal's absolute neutrophil count is less than 5000/μL.

Antitumor Antibiotics

Doxorubicin

Mechanism of Action Doxorubicin is an anthracycline glycoside derived from *Streptomyces peucetius*. It is directly cytotoxic, binding irreversibly with DNA and preventing both RNA and DNA synthesis. Cellular damage caused by doxorubicin results in enzyme-catalyzed, iron-mediated free radical formation, which produces further tissue damage. Ultimately, these effects result in induction of apoptosis in both normal and neoplastic cells. After IV administration, doxorubicin is metabolized in the liver to active and inactive metabolites. The drug is excreted primarily in the bile but persists in plasma for prolonged periods.

Spectrum of Activity Doxorubicin has been proved to be effective in the treatment of a number of tumors of the dog and cat, including lymphoma, leukemias, and certain sarcomas and carcinomas (Berg et al., 1995; Moore et al., 1996; Valerius et al., 1997; Ogilvie et al., 1989; Jeglum and Wheareat, 1983). It appears that doxorubicin may be synergistic with cyclophosphamide in the treatment of some sarcomas (Sorenmo et al., 1993), and it is combined with cytosine arabinoside as an extremely effective (although very myelosuppressive) protocol for leukemia.

Preparations Doxorubicin is available for IV use only in vials of 10, 20, and 50 mg.

Side Effects Cardiotoxicity is generally the dose-limiting factor for doxorubicin administration in dogs (Mauldin et al., 1992); it occurs from free-radical damage to the myocardium, with oxidation and death of myocardial cells in the presence of iron. Doxorubicin is an active iron chelator, and the resulting iron-doxorubicin complex catalyzes free-radical reactions, leading to myocardial damage. Acute cardiac toxicity may occur at any time and after any dosage; it commonly takes the form of an arrhythmia, which resolves with time in most animals. Arrhythmias are more common if there is previous cardiac disease, previous or concurrent thoracic irradiation, or concurrent cyclophosphamide administration. The second form of cardiac toxicity induced by doxorubicin is congestive heart failure, with myocardial degeneration and cardiac muscle fibrosis leading to heart failure; this generally occurs with cumulative doses greater than 240 mg/m^2.

Once congestive heart failure induced by doxorubicin is present, patients may respond to aggressive therapy for heart failure, but some patients will die despite all treatment. Many attempts have been made in humans to diagnose incipient cardiac toxicity before clinical manifestations of heart failure begin, but it remains impossible to predict which patients will develop these changes. Echocardiographic measurement of ventricular fractional shortening and serial electrocardiography are probably the best methods to monitor dogs and cats that are receiving treatment with doxorubicin.

Both humans and dogs have shown a great deal of individual variation in susceptibility to doxorubicin-induced cardiotoxicity. Even though clinical cardiac disease may not be evident after treatment with doxorubicin, subclinical damage to the heart is common. In a study of 115 children with lymphoblastic leukemia treated with doxorubicin and followed for many years, 57% had abnormal cardiac function later in life (Lipshultz et al., 1991). The EDTA-derivative drug ICRF-187 (dezrazoxane), given at 0.8 mg/kg 30 minutes before doxorubicin administration, apparently decreases cardiotoxicity without reducing cancer cell cytotoxicity (Imondi et al., 1996), but no large clinical trials of this compound in dogs or cats with cancer have been reported. Dezrazoxane acts as a cardioprotectant by chelating iron, helping to prevent the free radical-induced damage caused by doxorubicin; the product is not commercially available at this writing.

Although cats do not generally show clinical cardiac disease associated with doxorubicin treatment, histologic and echocardiographic evidence of damage to the myocardium occurs in cats treated with cumulative doses of 170 to 240 mg/m^2 (O'Keefe et al., 1993). Renal damage also occurs in cats with chronic treatment with doxorubicin; this is manifested by azotemia, dilute urine, and gradually decreasing creatinine clearance values during the course of administration (Cotter et al., 1985). Another serious side effect in cats is the profound anorexia that may accompany administration of doxorubicin at the conventional dose given to dogs (30 mg/m^2); cats given this dose do not act as though they are nauseated, but may not eat voluntarily for weeks, sometimes requiring placement of a feeding tube. Small dogs weighing less than 10 kg may also experience unexpected nausea and anorexia at this treatment dose. For cats and small dogs, a doxorubicin dose of 1 mg/kg has proved to be much better tolerated.

Myelosuppression may occur several days after administration, usually beginning on day 4. Peak action on the bone marrow occurs from days 10 to 14. Because doxorubicin has a high affinity for mast cells, causing them to degranulate, anaphylaxis, urticaria, generalized erythema, and head-shaking have been seen in the dog. To prevent this, the patient may be premedicated with antihistamines and steroids before administration. Alopecia may also occur in susceptible breeds of dogs.

Extreme phlebitis and necrosis occur if doxorubicin is extravasated. This necrosis begins 1 to 2 weeks after the drug is extravasated and continues for 1 to 4 months. Doxorubicin also produces an unusual "radiation recall" effect; if previous radiation damage has occurred, even years before, doxorubicin administration will cause its recurrence. This is not likely to be a problem in dogs and cats because radiation therapy to the thorax is rarely performed in these species, but it is often a serious complication of doxorubicin treatment in humans. Radiation to the thoracic cavity (when the heart is in the radiation field) may also potentiate the cardiotoxicity of doxorubicin, which could be an important consideration for dogs and cats with thymoma or mediastinal lymphoma.

Dosing Regimen Although the conventional dose of doxorubicin for medium-sized to large dogs is 30 mg/m^2 given every 3 weeks, this dose in very small dogs or cats may produce profound myelosuppression and anorexia. For this reason, the dose for very small animals (less than 10 kg) should be reduced to 1 mg/kg every 3 weeks. Doxorubicin should be administered slowly into the tubing of a freely running IV infusion of saline or 5% dextrose solution. The tubing should be attached to a catheter that was placed on the "first stick" to avoid any leaking of drug through holes in the vein. *At least* 5 minutes should be taken to give the drug. Alternatively, doxorubicin may be mixed in a small volume of saline (50 to 100 mL) and dripped intravenously over 20 to 30 minutes. Doxorubicin is physically incompatible with many other drugs, including heparin, aminophylline, cephalothin, dexamethasone, diazepam, hydrocortisone, and furosemide, so care should be taken not to give other drugs through the same line during the doxorubicin infusion.

Doxorubicin Analogues

Mechanism of Action Because doxorubicin is very cardiotoxic, much effort has been devoted to development of analogues that might have less toxicity but that would maintain the level of tumor response. Epirubicin (4′-epidoxorubicin) is an analogue that has been claimed to be less cardiotoxic in humans for equivalent doses. The mechanism of this drug is similar to that of doxorubicin. Idarubicin (4-demethoxydaunorubicin) is another anthracycline glycoside that is unusual in that it is the only antitumor antibiotic that can be given orally.

Spectrum of Activity The spectrum of canine and feline tumors that will respond to epirubicin therapy is probably similar to that for doxorubicin. Epirubicin's principal use has been as a single agent for dogs with canine lymphoma; response rate and duration of response are not significantly different from what would be expected with doxorubicin therapy (Vonderhaar et al., 1993). Idarubicin has been used orally for cats for maintenance therapy of lymphoma after remission is obtained with other drugs (Moore et al., 1995).

Preparations Epirubicin is not commercially available at this time. Idarubicin is unfortunately only commercially available in an injectable form, in 5-, 10-, and 20-mg vials.

Side Effects The claim that epirubicin has an advantage over doxorubicin in lessened toxicity has not proved to be particularly impressive. Myelosuppression is similar, with the neutrophil nadir seen 10 days after administration. A significant number of dogs treated with epirubicin still show evidence of cardiac toxicity, as measured by ventricular fractional shortening on echocardiography. Idarubicin may produce gastrointestinal signs and myelosuppression in treated cats, and dose modification may be necessary. Because idarubicin is very cardiotoxic in humans, it should be presumed that it has the same effect in dogs and cats; appropriate precautions and monitoring should be considered.

Dosing Regimen Epirubicin is given intravenously at a dose of 30 mg/m² for dogs weighing more than 10 kg and 1 mg/kg for dogs less than 10 kg. Similar precautions for administration to those taken with doxorubicin should be followed. Idarubicin has been given orally at 2 mg/cat per day for 3 days once every 3 weeks; injectable doses of idarubicin for dogs and cats have not been reported.

Dactinomycin (Actinomycin D)

Mechanism of Action Dactinomycin is one of the actinomycins, a group of antibiotics produced by various species of *Streptomyces*. The drug binds to DNA by intercalation and causes single-strand DNA breaks. Ultimately, dactinomycin causes apoptosis in susceptible tumor cells. As with doxorubicin, drug resistance to dactinomycin is caused by overexpression of P-glycoprotein; it is therefore unlikely that a response to dactinomycin will be seen in lymphomas in which the tumor cells have become resistant to doxorubicin.

Spectrum of Activity Dactinomycin has chemotherapeutic activity against canine lymphoma; activity has been seen in some drug-resistant lymphomas but generally only when the tumor is not yet doxorubicin resistant. Partial responses have been seen with dactinomycin treatment of nephroblastoma and botryoid rhabdomyosarcoma in the dog. Certain carcinomas may also respond, including anal sac adenocarcinoma, squamous cell carcinoma, thyroid carcinoma, and transitional cell carcinoma (Hammer et al., 1994b). The principal use of dactinomycin, however, is as a substitute for doxorubicin when a potentially cardiotoxic cumulative dose of doxorubicin has been reached and it is desirable to continue administration of an antitumor antibiotic.

Preparations Dactinomycin is administered intravenously and is supplied in vials containing 0.5 mg.

Side Effects Dactinomycin is extremely necrotizing when extravasated, similar to the effects produced by doxorubicin; it must be given through a "first-stick" catheter. Minimal myelosuppressive activity is noted when the drug is given as a solitary agent. Nausea and vomiting may occasionally occur during the first few hours after administration but may be partially prevented by administration of chemoreceptor trigger zone-blocking antiemetic agents. As with doxorubicin, dactinomycin potentiates the effects of radiation therapy and has a "radiation recall" effect. Cardiotoxicity is extremely rare with this drug.

Dosing Regimen Dactinomycin is given intravenously at a dose of 0.5 to 1 mg/m² once every 3 weeks. Because it is extremely corrosive to soft tissue, catheter placement should be meticulous. The calculated dose should be mixed with normal saline or 5% dextrose in water and dripped intravenously over 20 to 30 minutes.

Bleomycin

Mechanism of Action Bleomycin is an antitumor antibiotic derived from a strain of *Streptomyces* first isolated from the soil of a Japanese coal mine. Its cytotoxic effect is mediated by DNA binding and fragmentation, with single-strand and double-strand breaks. Interestingly, bleomycin seems to be more damaging to nonproliferating cells than to those actively proliferating. It has a unique lung toxicity in most animal species studied.

Spectrum of Activity Bleomycin is most effective for treatment of squamous cell carcinoma in cats and dogs (Buhles and Theilen, 1973); remissions are usually partial and of short duration, however. Recently, impressive results were obtained with intralesional injections of bleomycin into acanthomatous epulides in three dogs (Yoshida et al., 1998). These benign oral tumors are generally treated with surgical removal, sometimes involving a partial mandibulectomy or maxillectomy. The tumors were markedly smaller after three weekly bleomycin injections and had disappeared by 8 to 10 injections. No recurrence was noted in any of the cases during the follow-up periods, which ranged from 1 to 2 years. Bleomycin is also effective in humans as a sclerosing agent in the treatment of malignant pleural effusion, but there are no reports of this use in dogs or cats.

Preparations Bleomycin is given intravenously or by intralesional or intracavitary injection; it is supplied in 15-mg or 30-mg vials.

Side Effects Unlike the other antitumor antibiotics, myelosuppression is unlikely with bleomycin. Chronic administration of bleomycin to dogs every other day for more than 8 months resulted in the development of a pneumonitis, which progressed to pulmonary fibrosis (Schaeppi et al., 1974). The earliest symptom was dyspnea, with patchy opacities of the lung fields noted on radiographs. Microscopic changes included squamous metaplasia of the bronchiolar epithelium, fibrinous edema, and a diffuse interstitial fibrosis. Cutaneous ulceration and loss of nails also occurred in these dogs. Because bleomycin for clinical patients is principally used for short-term palliation of tumors, none of these chronic changes is likely to occur in clinical patients.

Dosing Regimen Bleomycin is given subcutaneously at a dose of 10 to 20 U/m² once weekly.

Mitoxantrone

Mechanism of Action Mitoxantrone is a derivative of anthracene and is related to doxorubicin and daunorubicin.

It intercalates into DNA and causes cross-linking, with inhibition of both DNA and RNA synthesis. It is cell cycle specific but phase nonspecific.

Spectrum of Activity Partial and complete remissions have been reported when mitoxantrone is used as a solitary chemotherapeutic agent for lymphoma (Ogilvie et al., 1991a). Because the drug is very expensive, it is not generally used for induction or maintenance therapy. Its principal use is for lymphomas whose tumor cells are resistant to other drugs; a response rate of 26% can be expected (Moore et al., 1994). Rare partial remissions and even rarer complete remissions are associated with administration of mitoxantrone to dogs and cats with various carcinomas and sarcomas, but the drug's use for tumors other than lymphoma has been generally disappointing.

Preparations Mitoxantrone is supplied in 20-, 25-, and 30-mg vials for IV use only.

Side Effects Side effects of mitoxantrone administration are mild to moderate gastrointestinal toxicity and myelosuppression. Although the myelosuppression associated with mitoxantrone is generally not marked, some dogs and cats will develop dangerously low neutrophil and platelet counts; for this reason, it may be prudent to begin treatment at the lower end of the dose range, with gradual escalation of the dose as treatment proceeds. Extravasation of the drug may result in severe local reactions, including ulceration and cellulitis. Although mitoxantrone is a relative of doxorubicin, its cardiotoxicity in dogs appears to be much less; no clinical evidence of cardiac effects was noted in a study of mitoxantrone administration in 129 dogs with different malignancies (Ogilvie et al., 1991b). Mitoxantrone does, however, induce both acute and chronic congestive heart failure in humans, and it is therefore probably not a good choice for dogs or cats in which the maximum safe dose of doxorubicin has been reached or in patients with pre-existing cardiac disease. A blue-green color may be noted in the sclera and urine of treated animals after therapy.

Dosing Regimen The dose of mitoxantrone for dogs and cats is 5 to 6.5 mg/m^2 given once every 3 weeks. The drug is diluted to at least 0.5 mg/mL in sterile saline and is given through a catheter over at least 3 minutes.

Antimetabolites

Methotrexate

Mechanism of Action Methotrexate is one of the antimetabolites, which as a class act as structural antagonists of normal metabolites or as co-factors of nucleic acids, generally having their greatest effect on cells in the S phase of the cell cycle. Methotrexate exerts its cytotoxic effect by competing for a binding site on the enzyme dihydrofolate reductase. This reversible binding prevents the synthesis of folate, which is important in the production of the purine nucleotides and thymidine. An "antidote" for methotrexate cytotoxicity is leucovorin (citrovorum factor), which provides folate for biochemical activity in the cell. Methotrexate is principally eliminated in urine; in humans, 80% to 90% of the administered dose is excreted unchanged in the urine within 24 hours. Assessment of renal function is important before administration of methotrexate, and dose modification for patients with compromised renal function may be necessary to prevent toxicity due to delayed drug clearance. Because the antimetabolites have a short half-life in the body, they are most effective when given by continuous infusion, thus killing cells as they enter the S phase; however, a protocol for safe and effective continuous intravenous infusion of methotrexate has not been published for the dog.

Spectrum of Activity Although methotrexate has been widely used in human oncology, often at very high doses with "leucovorin rescue," it has found only limited use in veterinary medicine as a part of combination protocols for lymphoma.

Preparations Methotrexate sodium may be administered intramuscularly, subcutaneously, or intravenously; the product for injection is available in 20-, 50-, 100-, 200-, and 250-mg and in 1-g vials. For oral administration, it is supplied as 2.5-mg scored tablets. Leucovorin calcium is available in vials of 100 mg for parenteral administration as well as 5- and 15-mg tablets for oral administration.

Side Effects Gastrointestinal side effects are the most important toxicities produced by methotrexate, with nausea occurring commonly. Oral ulceration and diarrhea may also be seen, and methotrexate should be used with great caution or not at all for patients with ulcerative colitis. Myelosuppression is mild at low dosage ranges. With long-term, low-dose therapy, hepatic dysfunction is a significant problem in humans, and methotrexate hepatotoxicity has been reported in the dog (Pond, 1982). Because nonsteroidal anti-inflammatory drugs and aspirin may decrease renal excretion of methotrexate and thus increase its toxicity, these drugs should not be given along with methotrexate. Concurrent administration of methotrexate with a trimethoprim/sulfa antibiotic would be likely to lead to severe folate deficiency and therefore increase the severity of myelosuppression.

Dosing Regimen The oral dose of methotrexate is 2.5 mg/m^2 given daily for 5 days followed by a 2-day rest period. This is repeated weekly until remission is achieved; 10 mg/m^2 given twice weekly followed by a 7-day rest period would be another acceptable protocol. Toxic hematopoietic effects may be reversed by 6 to 12 mg of leucovorin given subcutaneously four times a day for four doses.

Cytosine Arabinoside

Mechanism of Action Cytosine arabinoside (cytarabine, ara C) is highly specific for the S phase of the cell cycle, and its effectiveness is therefore dependent on maintaining constant drug levels; continuous infusion or frequent, closely spaced doses are necessary for successful treatment of tumors using this drug. Cytosine arabinoside is transported into the cell and metabolized to 5′-triphosphate ara C, which inhibits DNA polymerase. The metabolite is then incorporated into DNA, preventing templating from DNA and inhibiting DNA repair. Cytosine arabinoside is one of the few chemotherapeutic drugs that crosses the blood-brain barrier easily, and it can therefore be used to treat central nervous system lymphoma, as well as to kill leukemic cells in the cerebrospinal fluid.

Spectrum of Activity In veterinary oncology, cytosine arabinoside is generally used in combination protocols for treatment of canine and feline lymphoma. It may also be used to treat acute leukemias of both lymphoid and nonlymphoid types (Hamilton et al., 1991b).

Preparations Cytosine arabinoside is available for IV or subcutaneous injection in vials containing 100 mg, 500 mg, 1 g, or 2 g.

Side Effects Because of its specificity for cycling cells in the S phase, cytosine arabinoside usually causes myelosuppression, with the degree of myelosuppression increasing with the frequency and duration of administration. When large doses are given by bolus injection intravenously rather than by infusion, nausea and vomiting are common.

Dosing Regimen For lymphoma, single-agent cytosine arabinoside may be given at a dose of 600 mg/m^2 intravenously once a week; lower doses of 200 to 300 mg/m^2 weekly should be used if cytosine arabinoside is part of a combination-drug protocol. For treatment of acute leukemias, 100 mg/m^2 per day given by continuous infusion or divided into four daily subcutaneous injections repeated for 5 days will produce the greatest response against leukemic cells. *Note:* Cytosine arabinoside, especially when used with doxorubicin, is extremely effective in clearing the bone marrow of tumor cells in leukemia patients. In general, patients will have a period of severe bone marrow aplasia for 7 to 21 days after the cycle is completed, often with neutrophil numbers less than 1000/μL and platelet counts less than 50,000/μL. Infection or hemorrhage may ensue during this period, and treatment with rhG-CSF should ideally be used daily along with chemotherapy.

5-Fluorouracil

Mechanism of Action 5-Fluorouracil is a pyrimidine analogue that exerts its cytotoxic effect by inhibiting thymidylate synthetase and thus DNA synthesis and, to a lesser extent, RNA synthesis. The cytotoxic effects of 5-fluorouracil are greatest on cells in the G_1 and S phases; with longer periods of exposure to the drug, cells in other phases of the cell cycle may also be killed. Because the drug is erratically absorbed from the gastrointestinal tract, it is generally given intravenously. It is also available as a topical cream.

Spectrum of Activity In humans, 5-fluorouracil is the drug of choice for gastrointestinal carcinomas; it is effective in the palliative management of carcinoma of the colon, rectum, stomach, and pancreas. In the dog and cat, however, it has found limited usage because of neurotoxicity.

Preparations For injection, 5-fluorouracil is available in 500-mg vials. For topical use, it is supplied in 25-g tubes.

Side Effects 5-Fluorouracil treatment in dogs is often accompanied by central nervous system reactions (behavior changes such as barking incessantly, running in circles, aggressiveness) (Harvey et al., 1977; Hammer et al., 1994a; Dorman et al., 1990); continuing administration of the drug in the face of such neurologic signs may lead to seizures and death (Okeda et al., 1984). Mild myelosuppression and nausea are sometimes noted. Stomatitis and mucositis resembling pemphigus vulgaris may be seen in dogs receiving several weeks of treatment. Because unprovoked rage, extreme dementia, and sudden death may occur in cats treated with 5-fluorouracil, it should not be used in this species (Theilen, 1987).

Dosing Regimen 5-Fluorouracil may be given intravenously at 150 to 200 mg/m^2 for 3 days and then 100 mg/m^2 on the fifth, seventh, and ninth days. No drug is given on the fourth, sixth, and eighth days. Monitor blood count at the end of the cycle and before the next cycle begins. If gastrointestinal signs, stomatitis, neurologic signs, or falling white blood cell count (less than 4000/μL) are noted, discontinue the drug. Generally, cycles of 5-fluorouracil are repeated monthly. In the dog, 5-fluorouracil is useful for small skin carcinomas or solar keratosis as a topical cream. This is applied twice daily until there is an erosive inflammatory response with ulceration (usually 2 to 4 months), at which time use of the drug should be stopped. Healing may take several months after the topical treatment is discontinued. Owners should wear gloves while administering the cream. *5-Fluorouracil should not be used in cats.*

Hydroxyurea

Mechanism of Action Hydroxyurea inhibits ribonucleotide reductase, leading to depletion of essential DNA precursors; cells accumulate in the S phase of the cell cycle.

Spectrum of Activity Hydroxyurea is used for the palliative treatment of chronic myelogenous leukemia (Leifer et al., 1983), eosinophilic leukemia/hypereosinophilic syndrome in cats (Hamilton, 1998), and basophilic leukemia in the dog (MacEwen et al., 1975). It is effective for management of polycythemia vera in the dog and cat (Peterson and Randolph, 1982).

Preparations Hydroxyurea is available in 500-mg capsules for oral administration.

Side Effects Side effects of hydroxyurea are generally mild and well tolerated and include nausea and myelosuppression. In the dog, loss of toenails may occur with chronic hydroxyurea administration, and a seborrhea sicca-like syndrome may be noted.

Dosage Regimen Hydroxyurea is given orally at a dose of 35–50 mg/kg once daily for 7 to 10 days and then every other day until remission. After remission is obtained (leukemic cell counts are reduced in leukemia patients or packed cell volume is normal in patients with polycythemia vera; neutrophil and platelet counts are in the normal range), a dose of hydroxyurea is determined that will maintain remission. In some patients, daily administration of hydroxyurea will continue to be necessary but at a lower dose: 20 mg/kg per day, for example. In other patients, administration of a higher dose (such as 50 to 75 mg/kg) twice weekly will be adequate. The dose of hydroxyurea is "titrated" to the patient's complete blood count results.

Platinum Drugs

Cisplatin

Mechanism of Action Cisplatin is a very useful drug in human and veterinary oncology. Its complete chemical name is *cis*-dichlorodiammineplatinum (DDP), reflecting the fact that it is formed by platinum surrounded by chlorine and ammonia atoms in the *cis* position of the horizontal plane. Its cytotoxic effects are considered to be due to alkylation of DNA.

Spectrum of Activity Cisplatin has been shown to produce objective responses in many types of carcinomas in the dog (Fineman et al., 1998; Himsel et al., 1986; Shapiro et al., 1988; Knapp et al., 1988). Administration of cisplatin as an adjuvant agent with amputation in canine osteosarcoma has produced significantly longer survival than is seen with amputation alone (Thompson and Fugent, 1992; Kraegel et al., 1991). Complete remission has also been seen in dogs with metastatic seminoma. Intracavitary cisplatin has resulted in complete and durable palliation of pleural effusion due to mesothelioma and carcinomatosis of unknown origin (Moore et al., 1991); intraperitoneal treatment with cisplatin for patients with carcinomatosis due to ovarian carcinoma would also be reasonable.

Preparations Cisplatin is available for parenteral injection in 50-mg and 100-mg vials.

Side Effects *Treatment of cats with cisplatin is contraindicated*; dyspnea and death with pulmonary edema occur within 48 to 96 hours after cisplatin administration, even with only one treatment (Knapp et al., 1987). Cisplatin is *extremely* nephrotoxic in the dog, especially if prehydration is not performed with treatment. Before each treatment, blood urea nitrogen and creatinine evaluations and a urinalysis should be performed; elevation of blood urea nitrogen and creatinine in the face of a dilute urine should signal the onset of renal toxicity, and additional treatments of cisplatin should not be given. Carboplatin may be substituted for cisplatin because it is much less nephrotoxic.

Acute gastrointestinal toxicosis with nausea, anorexia, and vomiting is common after cisplatin administration, usually beginning 2 to 4 hours after treatment (most dogs will vomit for less than 6 hours); the severity of the emesis can be decreased with administration of butorphanol or ondansetron.

Hypomagnesemia, hypocalcemia, hyponatremia, hypokalemia, and hypophosphatemia may occur after repeated doses of cisplatin, probably due to renal tubular damage. Myelosuppression is generally mild but lengthy, with a double neutrophil nadir at 6 and 15 days post-treatment. A complete blood count should be performed before administration of each cisplatin treatment; neutropenia may persist as long as 21 to 28 days after a single treatment, causing delay in the administration of the next course of therapy.

Dosing Regimen The dose for cisplatin in dogs is 60 to 70 mg/m^2 given once every 21 days. An antiemetic such as butorphanol (0.4 mg/kg) is generally given before the treatment is begun; another dose may be given 2 hours later if vomiting becomes a problem. Intravenous saline solution should be given to prehydrate the patient at the rate of 25 mL/kg per hour for 3 hours (18.3 mL/kg per hour for 4 hours in dogs that might become volume overloaded), followed by a 20-minute intravenous infusion of cisplatin mixed in saline. This is followed by additional fluids given for 1 more hour (2 hours for a heart failure patient because the fluid rate is lower) at the same rate. Needles or IV sets containing aluminum parts that may come into contact with cisplatin should not be used for preparation or administration because a precipitate will form, causing loss of potency. For intracavitary treatment of mesothelioma or carcinomatosis, the animal is prehydrated with intravenous saline as above. Cisplatin 50 mg/m^2 is diluted in 0.9% NaCl to a total volume of 1 L/m^2 for intraperitoneal therapy or 250 mg/m^2 for intrapleural delivery. The solution is warmed to body temperature and instilled through an aseptically placed catheter over 15 minutes, and post-therapy hydration is performed as above. Treatments are repeated once every 4 weeks as needed to maintain remission. *Do not give cisplatin to cats.*

Carboplatin

Mechanism of Action Because of cisplatin's effectiveness in the treatment of many tumors, great interest developed in the search for another platinum compound that would maintain the same level of cytotoxicity but that would not be as toxic to the patient. Carboplatin was developed at Michigan State University to fulfill these requirements; it is similar to cisplatin in pharmacology and antitumor effects. The major route of elimination of carboplatin, like cisplatin, is renal excretion; however, carboplatin causes significantly less renal toxicity, so fluid diuresis before and after administration is not required.

Spectrum of Activity In the treatment of human cancers, carboplatin and cisplatin appear to share the same spectrum of activity; this is presumed to be the case also for the dog. Because of its very different level of toxicity compared with cisplatin, carboplatin is a logical alternative to cisplatin for patients with renal disease or patients with cardiac disease, for which the large amount of fluids administered with cisplatin treatment might be dangerous. Carboplatin is also safe to use in cats, unlike cisplatin, and intralesional injections of a carboplatin-oil emulsion into squamous cell carcinomas of the nasal planum in cats have resulted in objective responses and apparent cures in some (Theon et al., 1996).

Preparations Carboplatin is available for intravenous infusion in 50-, 150-, and 450-mg vials.

Side Effects Carboplatin is significantly less nephrotoxic than cisplatin and only rarely produces nausea and vomiting. Dose-dependent neutropenia and thrombocytopenia are common, however, and the myelosuppression produced by the drug may be prolonged. In general, carboplatin treatment should not be repeated until neutrophil and platelet counts are in the normal range. Toxicity in the cat is principally myelopsuppression, as in the dog (Hahn et al., 1997). Although carboplatin has limited renal toxicity, concomitant treatment with aminoglycosides may result in enhanced kidney toxicity as well as hearing loss.

When carboplatin in purified sesame oil has been used to treat squamous cell carcinomas in cats intralesionally, systemic toxicosis was not observed in any of the cats. Plasma concentrations of carboplatin did not significantly increase during the course of treatment. Water-in-sesame-oil emulsions have been shown to be effective carriers for intratumor administration of antineoplastic agents, preserving drug activity and enhancing concentration of drug locally by allowing slow release into tissues. This allows for intensification of carboplatin chemotherapy without dose-limiting adverse effects.

Dosing Regimen Carboplatin is given as a 15 to 20 minute IV infusion at a dose of 250 to 300 mg/m^2 once every 3 to 4 weeks for dogs; unlike cisplatin, IV carboplatin is safe for cats at a dose of 150 to 200 mg/m^2 once every 3 to 4 weeks. As in cisplatin, aluminum reacts with carboplatin, causing a precipitate; needles with aluminum parts should not be used for the preparation or administration of carboplatin.

For intralesional injection of the nasal planum in cats with squamous cell carcinoma, treatments should be done with the animal under general anesthesia due to the pain that the injection procedure is likely to produce. Carboplatin is prepared in a water/oil emulsion that includes 10 mg of carboplatin in 1 mL of water mixed with 2 mL of sterile, purified, medical-grade sesame oil; a viscous, yellowish liquid is created by this mixture. The emulsion is injected into the tumor and surrounding borders so that approximately 1.5 mg of carboplatin is injected per cubic centimeter of tumor tissue. Four weekly doses are given.

Miscellaneous Drugs

L-Asparaginase, Pegaspargase

Mechanism of Action L-Asparaginase is an enzyme that is derived from *Escherichia coli* and that exploits a qualitative biochemical defect found in some tumor cells. In acute lymphoid leukemia and lymphoma, most malignant cells are dependent on an extracellular source of asparagine for survival. Normal cells, however, are able to synthesize asparagine, and thus are affected less by the rapid extracellular depletion of asparagine produced by L-asparaginase. Although most susceptible tumors respond with dramatic reduction in size with the first administration of L-asparaginase, drug resistance of these cells develops quickly; a population of tumor cells is selected in which the enzyme asparagine synthetase is present, asparagine can be made intracellularly, and the tumor cells are therefore unaffected by the enzyme's administration. Pegaspargase is modified from L-asparaginase by covalently conjugating monomethoxypolyethylene glycol to the enzyme, forming the active ingredient PEG-L-asparaginase; pegaspargase produces fewer hypersensitivity reactions with administration than conventional L-asparaginase.

Spectrum of Activity L-Asparaginase is principally useful in treatment of lymphoma and lymphoid leukemia. Because hypersensitivity and drug resistance develop relatively rapidly, L-asparaginase is a useful agent for induction of remission or in relapsed lymphoid malignancies, but it should not be employed as a part of a maintenance protocol.

Preparations L-Asparaginase is available in vials containing 10,000 IU for parenteral administration. Pegaspargase is supplied in vials containing 3,750 IU.

Side Effects Because asparaginase is a foreign protein, severe allergic reactions may be seen on repeated administration. In humans, this is a significant problem, and it is recommended that an intradermal skin test be performed if the drug is to be given repeatedly; in the dog, however, anaphylactoid reactions are rare (Ogilvie et al., 1994). Extreme facial edema and swelling and pain at the site of injection have been noted in occasional dogs within 24 hours after L-asparaginase administration, however, presumably as a manifestation of an allergic reaction to the drug.

Pegaspargase was developed in an attempt to decrease the allergic reactions associated with administration of the drug; it is conjugated with polyethylene glycol and is indicated when L-asparaginase therapy is necessary despite a hypersensitivity reaction to previous treatment. Studies with the PEG-modified enzyme in dogs have indicated that it is also active against lymphoma (MacEwen et al., 1992). The necessity for its use in veterinary medicine is limited because of the comparative rarity of allergic drug reactions with the use of conventional L-asparaginase.

Side effects associated with the administration of L-asparaginase in the dog are quite rare. Hyperamylasemia occurs in some patients and may progress to acute necrotizing pancreatitis (Hansen, 1982). L-asparaginase administration in humans causes a temporary but fairly dramatic inhibition in protein synthesis by the liver, resulting in reduced levels of clotting factors. Levels of antithrombin III and fibrinogen in dogs with lymphoma after L-asparaginase administration have not been found to be abnormal, however, and other clotting parameters were not significantly affected either (Mandell, 1992; Rogers et al., 1992). Clinically important bleeding or thrombosis may occur in the dog but is extremely rare (Swanson et al., 1986). L-asparaginase deaminates extracellular asparagine to L-aspartic acid and ammonia. In patients with pre-existing hepatic disease or significant liver function abnormalities related to tumor infiltration, treatment with L-asparaginase may result in a syndrome resembling ammonia encephalopathy, with confusion and stupor. If serum ammonia levels are found to be high in these patients, treatment with lactulose should be instituted until signs abate.

Dosing Regimen Dosage is 10,000 to 20,000 IU/m^2 or 400 IU/kg (maximum dose is 10,000 IU) weekly or as part of a combination protocol. The drug may be given subcutaneously, intramuscularly, or by IV administration. If L-asparaginase is given intravenously, the drug should be given over a period of not less than 30 minutes through the side arm of an already running infusion of sodium chloride or 5% dextrose.

Piroxicam

Mechanism of Action Piroxicam is a nonsteroidal anti-inflammatory agent that has anti-inflammatory, analgesic, and antipyretic properties in animals; edema, erythema, and tissue proliferation can be inhibited by the administration of the drug. Piroxicam inhibits the generation of thromboxane B_2 in the blood of dogs by more than 70%, and more than 50% inhibition was maintained in most of the dogs for 48 hours (Galbraith and McKellar, 1991). The drug has also been reported to have antitumor activity in animal models and in metastatic tumors in humans. The exact mechanism for piroxicam's role in cancer treatment is not established at this time, but it is unlikely that the effects can be attributed to a direct cytotoxic effect (Knapp et al., 1995).

Spectrum of Activity Piroxicam has produced objective responses in several types of carcinomas, including transitional cell carcinoma (Knapp et al., 1994), squamous cell carcinoma, mammary adenocarcinoma, and in a dog with pulmonary metastatic carcinoma (Knapp et al., 1992). Its principal use is in palliation of transitional cell carcinoma of the urinary tract; relief of stranguria and hematuria often associated with transitional cell carcinoma may be seen for 4 to 11 months after beginning treatment.

Preparations Piroxicam is supplied as 10-mg and 20-mg capsules for oral administration.

Side Effects Serious gastrointestinal toxicity with mucosal ulceration and bleeding, sometimes with perforation, may occur with piroxicam administration, especially if the drug is given daily. If daily administration of piroxicam is necessary, concurrent misoprostol at a dose of 5 μg/kg orally three times a day should be considered to prevent gastrointestinal ulceration. Nephrotoxicity with renal papillary necrosis has also been reported with higher doses.

Dosing Regimen The dose is 0.3 mg/kg given orally once a day for 5 days and then every other day indefinitely, as long as efficacy is noted.

Corticosteroids

Mechanism of Action Several glucocorticoid hormones are used in the treatment of patients with cancer. In increasing order of potency, these are hydrocortisone, prednisone, and dexamethasone. The anti-inflammatory effects of these hormones may help to control pain in patients with terminal disease. Reduction of edema in the central nervous system with primary brain tumors or brain metastases occurs, especially with dexamethasone; barrier permeability within the tumor is decreased, thus reducing the rate of edema formation.

Corticosteroids are effective in lymphoid tumors by producing a direct lymphocytotoxic effect, apparently binding to intracellular receptors and inducing apoptosis. A population of steroid-resistant tumor cells (possibly lacking steroid receptors) develops rapidly if the steroid is used as a single agent, however, usually within 3 to 4 months after treatment of lymphoma begins. Because glucocorticoids are transported out of the cell by the multiple drug-resistance gene product P-glycoprotein, remission may be shorter and more difficult to achieve with certain other chemotherapeutic agents after steroid resistance develops (Price et al., 1991).

Spectrum of Activity Corticosteroids are most useful for their direct cytotoxicity in the management of lymphoma, lymphoid leukemias, thymoma, and plasma cell tumors. They are also important in the symptomatic management of mast cell tumors, shrinking these tumors by decreasing edema and inflammation and by reducing the eosinophilic and neutrophilic infiltrate commonly seen in these tumors. Whether neoplastic mast cells are actually killed by corticosteroid administration has not been determined. Corticosteroid administration may produce a dramatic improvement in clinical signs when used for patients with intracranial and spinal cord neoplasms, relieving signs of compression temporarily. These hormones are also useful in relieving the general debility, fever (noninfectious), and anorexia of cancer. Because corticosteroids produce a "euphoria," their administration to animals with terminal metastatic disease may improve quality of life transiently, even though tumor growth is not inhibited by the drug.

Preparations Prednisone and dexamethasone are available for oral and parenteral use in a variety of tablet and solution strengths. The drugs are also available in preparations for ophthalmic administration.

Side Effects Side effects associated with the high doses of corticosteroids used in cancer treatment are numerous. For most owners, polydipsia and polyuria are the side effects of lymphoma or mast cell tumor treatment in dogs that are most difficult to accept; methylprednisolone, although much more expensive, may produce less polydipsia and polyuria. Owners should also be warned of the ravenous appetite often associated with steroid administration in dogs and cats. Temporal muscle atrophy, gastrointestinal ulceration and perforation, impaired wound healing, endocrine alopecia, increased incidence of bacterial infections, acute necrotizing pancreatitis, and personality changes are all occasional side effects seen with steroid administration, especially in dogs. Owners should be warned not to discontinue steroid treatment suddenly if their pet has been receiving corticosteroids for longer than 2 weeks because the hypothalamic-pituitary-adrenal axis is probably suppressed at the high doses being given.

Dosing Regimen Steroids may be administered orally, subcutaneously, intramuscularly, or intravenously, depending on the patient's condition. A conventional dose of prednisone for treatment of lymphoma is 30 to 40 mg/m^2 orally once daily through induction and then on alternate days during maintenance. Edema induced by intracranial or spinal neoplasia may be treated with prednisone at the above dose or with dexamethasone at 0.1 mg/kg twice daily.

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19

Immunomodulators or Biologic Response Modifiers: Introduction and Miscellaneous Agents

Dawn Merton Boothe

- THE IMMUNE RESPONSE
- Immune Defenses
- Effectors
- Cellular Components
- Soluble Components
- Immunoglobulins
- Hypersensitivity Reactions
- Immunomodulatory Effects of Opioids
- CLASSIFICATION OF IMMUNOMODULATORY DRUGS
- IMMUNOMODULATION IN VIRAL AND NEOPLASTIC DISEASES
- Viral Diseases
- Neoplastic Diseases
- BIOLOGIC RESPONSE-MODIFYING DRUGS
- Immunosuppressant Drugs
  - Cyclosporin A
  - Tacrolimus
  - Mycophenolate Mofetil
  - Leflunomide
  - Hormones
  - Cytotoxic Drugs: Antimetabolites and Other Antineoplastic Agents
  - Gold Therapy
- Immunostimulant Drugs
  - Immunostimulants of Microbial Origin
  - Immunostimulants of Natural Origin
  - Synthetic Immunostimulants
  - Miscellaneous Immunostimulants
- TREATMENT OF SPECIFIC IMMUNE-MEDIATED DISEASES
- Type I Hypersensitivities
  - Anaphylaxis and Anaphylactoid Reactions
  - Allergic Respiratory Diseases
  - Atopy
- Type II Hypersensitivities: Antigen-Antibody Dependent Cytotoxicity
  - Immune-Mediated Hemolytic Anemia
  - Immune-Mediated Thrombocytopenia
  - Immune-Mediated Neutropenia
  - Dermatologic Disorders
- Type III Hypersensitivities: Immune Complex Disease
  - Systemic Lupus Erythematosus
  - Cutaneous Discoid Lupus Erythematosus
  - Rheumatoid Arthritis and Other Arthritides
- Type IV Hypersensitivities: The Delayed Response
  - Allergic Contact Dermatitis
  - Inflammatory Myopathies
  - Inflammatory Bowel Disease

THE IMMUNE RESPONSE

Immunomodulators, or biologic response modifiers, are agents or drugs that act to regulate or modify the host's immune response to a microbe, neoplasm, or inflammatory response. It is beyond the scope of this chapter to provide a comprehensive review of the immune system. A general overview follows. Cytokine biology can be reviewed more thoroughly in Chapter 20 or Aggarwal and Puri (1995), Nicola (1994), and Hilton (1994) and interferon biology in Tizard (1995).

Immune Defenses

Immune defenses are composed of the innate and adaptive systems. The innate systems are nonspecific in their response and are best exemplified by barriers provided by the integument, the gastrointestinal environment (acid pH and mucosal and epithelial barriers), the mucociliary tract of the respiratory system, and the intimate vasculature of selected organs such as the placenta, brain, and prostate. Other nonspecific defense mechanisms include fever and the antimicrobial actions of many secretions. The adaptive system is composed of two major mechanisms, cell-mediated immunity and humoral immunity, each accompanied by a variable number of cells and their chemical mediators. Some of the nonspecific components are also part of the adaptive immune system, including phagocytic circulating leukocytes and tissue macrophages, and secretions or body fluids such as interferon, complement, and leukocyte substances such as lysozyme. The primary targets of pharmacologic manipulation of the immune system are the adaptive arms of the immune system.

Both cell-mediated and humoral immune mechanisms are characterized by specificity toward antigenic epitopes expressed as molecular components of infectious organisms, foreign (transplanted) cells, or transformed (malignant) cells. Cytokines, including soluble growth and activation factors (Table 19–1), are a vital component of the adaptive response and are released and subsequently mediate the response of the various cell populations involved in both cell-mediated and humoral immunity (Diasio and LoBuglio, 1995). In addition to cytokines, a number of other molecules (such as adhesion or accessory molecules) are necessary as "second signals" for antigen processing, recognition, or response (Diasio and LoBuglio, 1995).

Table 19–1. Role of Selected Cytokines in the Immune Response

Cytokine	Response
Interleukin-1 (IL-1)	Stimulation of early bone marrow stem cells and lymphocyte precursors
Interleukin-2 (IL-2)	T-cell proliferation and generation of cytolytic "killer" cells
Interleukin-3 (IL-3)	Proliferation of bone marrow lineage cells, B and T cells
Interleukin-4 (IL-4)	Activation of B and T cells and macrophages
Interleukin-5 (IL-5)	Generation of eosinophils by bone marrow
Interleukin-6 (IL-6)	Proliferation of bone marrow and plasma cells
Interleukin-7 (IL-7)	Stimulation of B and T cells; synergistic with IL-2
Interleukin-8 (IL-8)	Chemotactic for neutrophils, B and T cells
Interleukin-9 (IL-9)	Proliferation of mast cells
Interleukin-10 (IL-10)	Inhibition of T cells
Interleukin-11 (IL-11)	Synergistic with IL-3
Interleukin-12 (IL-12)	Synergistic with IL-2
Interferon-α (IFN-α)	Activation of macrophages, T lymphocytes, and natural killer cell activity
Interferon-γ (IFN-γ)	Activation of macrophages and T cells, enhanced MHC expression
Granulocyte/macrophage colony, stimulating factor (GM-CSF)	Bone marrow proliferation and activation of antigen-presenting cells
Tumor necrosis factor (TNF-α,β)	Cytotoxic effect on tumor cells; stimulation of inflammation

From Diasio RB, LoBuglio AF: Immunomodulators: immunosuppressive agents and immunostimulants. In Hardman JG, Limbird LE (eds): Goodman and Gilman's The Pharmacological Basis of Therapeutics, 9th ed, pp 1291–1308. New York, McGraw-Hill, 1995.

Effectors

A brief synopsis of the events following infection to implementation of the immune response is as follows (Fig. 19–1). The antigen is exposed to an antigen-processing cell (APC), which includes dendritic cells (the principle APC), macrophages, and activated B cells (Diasio and LoBuglio, 1995). The antigen is identified by the APC as foreign and is subsequently phagocytized by the APC. The APC "processes" the antigen and "exhibits" it on the cell surface in a groove made by the major histocompatibility complex (MHC) molecule. Peptides derived from endogenous proteins synthesized within the cell complex (including those synthesized in response to viral stimuli) are expressed with class II MHC molecules on the cell surface, whereas exogenous proteins are expressed bound to a class I MHC groove for presentation (Diasio and LoBuglio, 1995).

A single APC surface may have tens of thousands of MHC molecules, each containing a different peptide; a single animal may have over 10^8 APCs. The APC migrates to the T-cell area of a lymph node and presents the antigen to naive CD4 T cells. If the APC contacts a CD4 T cell with a receptor that recognizes the antigen associated with the MHC, it becomes activated. The release of adhesion molecules causes the two cells to stick together, which facilitates interaction between the APC and the CD4. Cytokines move between the two cells, and production of interleukin-1 (IL-1) by the APC and IL-2 from the activated CD4 cell itself amplifies the sequelae of CD4 activation. The activated CD4 cell differentiates, proliferates, and produces a number of cytokines (see Table 19–1), which results in recruitment of other leukocytes, initiation of B-cell production of immunoglobulins, and formation of other T-cell colonies, including "memory" cells (Diasio and LoBuglio, 1995) (see Fig. 19–1).

Cellular Components

Two classes of lymphocytes are responsible for adaptive immunity (see Fig. 19–1). B lymphocytes must be programmed to respond to antigen exposure and, after activation to plasma cells, are responsible for the production of specific immunoglobulins (humoral response). T lymphocytes provide the primary regulation of the immune response. T-cell activity begins with specific antigen recognition by a receptor on the surface of the cell (Diasio and LoBuglio, 1995). T cells are further subdivided into several populations of cells based on their role in immunoregulation (see Fig. 19–1). Helper cell (CD4 T cells; Th cells) receptors recognize and bind to the peptide-MHC class II complex of APC cells. In response to IL-1, CD4 cells consequently proliferate and become primed as either Th1 or Th2 CD4 cells, which modulate further responses in both the humoral and cell-mediated arms. Migration of activated lymphocytes from lymph nodes to tissues is facilitated by adhesion molecules expressed by endothelial cells in tissues.

The TH1 subsets of CD4 produce interferon-γ (IFN-γ) and are responsible for generation of memory cells and activation of the T-cell–mediated response (see Fig. 19–1). The cell-mediated response occurs when activated CD4 (Th1) cells attract other cells (polymorphonuclear leukocytes, eosinophils, and monocytes) to support cellular killing; the result is referred to as *delayed hypersensitivity.* Activated CD4 cells also yield, in response to IL-2, CD8 cells that are responsible for the T-cell–mediated cytotoxic response. Receptors of the CD8 T cells recognize peptide-MHC class I complexes (generally associated with endogenous—including viral stimulated—peptides) on APC. Recognition of the CD8 receptor and subsequent interaction with CD4 cells results in the generation of cytolytic T cells. Cytolytic cells are capable of directly (without further interaction with CD4 cells) causing lysis of cells expressing the targeted specific peptide MHC complex (Diasio and LoBuglio, 1995).

Activation of the humoral system occurs when naive B lymphocytes with appropriate receptors (immunoglobulins) recognize an epitope in the intact foreign antigen. The antigen binds to the immunoglobulin, is ingested, and is processed such that it is expressed on the surface of the B

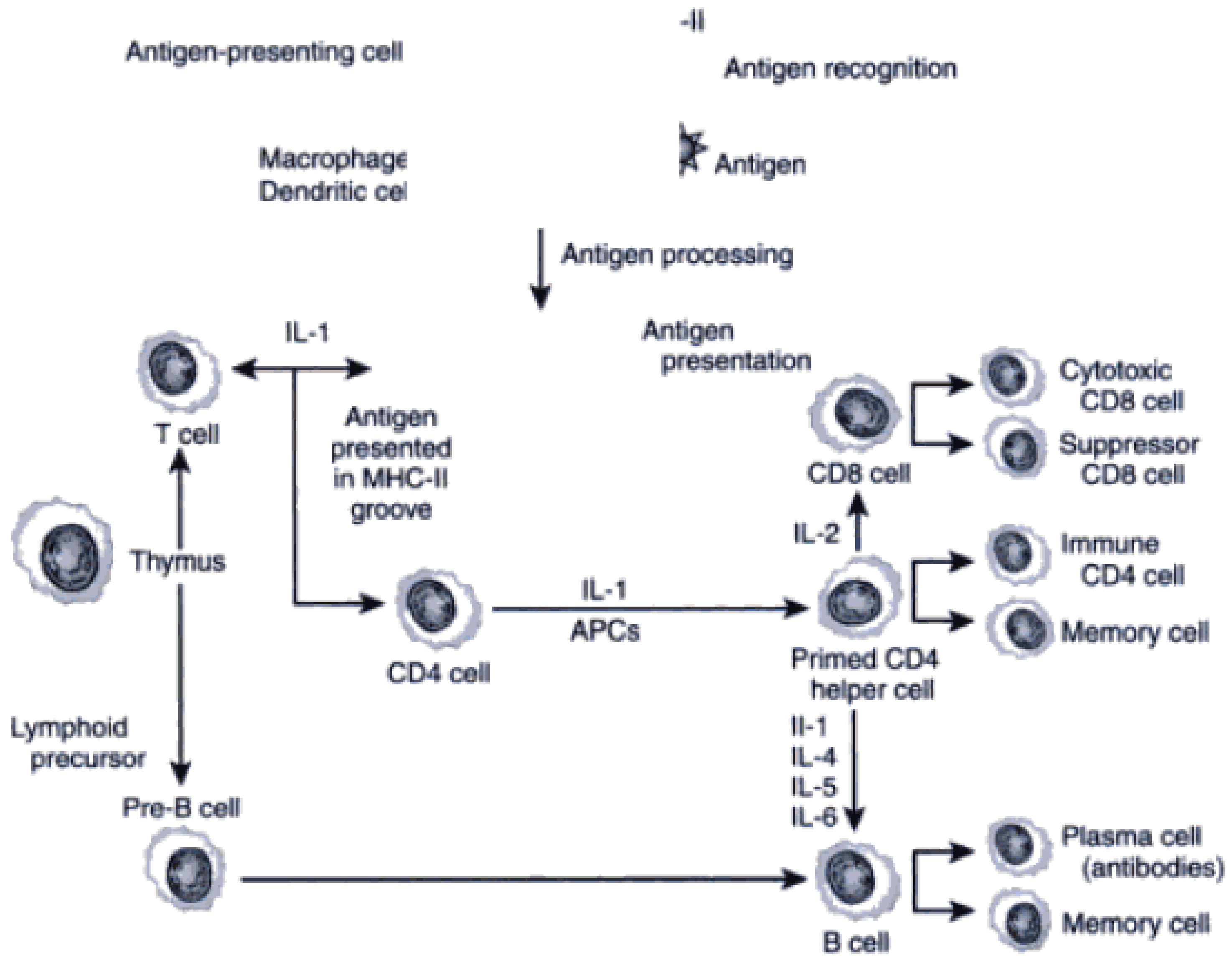

Figure 19–1. Overview of the immune response to antigen presentation. The antigen is presented to an antigen-presenting cell (APC), which processes the antigen and expresses its peptides in a groove located on the major histocompatibility complex (MHC) molecule. When presented to naive CD4 T cells with appropriate receptors, the helper cell becomes primed to form CD8 cells, capable of directly killing cells presently containing the antigen; Th1 cells, which result in the formation of memory T cells and T cells that attract other leukocytes (type IV hypersensitivity); or Th2 cells, which stimulate B-cell production of antibodies. A number of interleukins signal the activities; adhesion molecules (not shown) facilitate communication between cells as well as movement from lymph nodes through vascular endothelial cells into tissues. IL = interleukin; Th = T helper cell.

cell in association with the same MHC (class I or II) that presented the antigen initially (Diasio and LoBuglio, 1995). Binding of the immunoglobulin receptor with the peptide and subsequent interaction with a CD4 cell that recognizes the antigen in its MHC complex stimulates proliferation of B cells, their differentiation into plasma cells, and the secretion of antibodies able to bind the epitope. Immunoglobulin production is stimulated via IL-1, IL-4, IL-5, and IL-6 in B lymphocytes. The complete sequence occurs over 8 to 14 days and results in an anamnestic or secondary response. Generation of "memory" B and T cells provides a long-term mechanism for a rapid immune response on re-exposure to the epitope (antigen) (Diasio and LoBuglio, 1995).

An imbalance in the activities of CD4 Th1 and Th2 subsets may be responsible for the onset or exacerbation of immune-mediated diseases. Increased concentrations of Th1 (and decreased Th2) are associated with response to viral and fungal infections, whereas increased concentrations of Th2 (and decreased Th1) are associated with increased production of immunoglobulin E and A antibodies. Autoimmune diseases are associated with a predominance of Th1. Imbalances also have been associated with resistance to infectious disease and malignancy (Rabin, 1998).

Soluble Components

Soluble components of the immune response include the cytokines previously described, immunoglobulins described below, and the complement cascade. The complement cascade is a major effector mechanism of the immune response. The cascade results in highly amplified events that interact with other physiologic cascades, including the coagulation pathway, kinin formation, and fibrinolysis (Gorman, 1995). Consequences of complement activation include opsonization, the release of biologically vasoactive peptides, and cellular lysis. Cell-mediated cytotoxicity is implemented by cytotoxic T lymphocytes, natural killer cells (derived from lymphocytes), and antibody-dependent cell-mediated cytotoxicity (ADCC), mediated by a variety of cells that express surface Fc receptors. Effector cells of ADCC include monocytes, neutrophils, eosinophils, and selected cytotoxic T cells and natural killer cells.

Immunoglobulins

Five classes of immunoglobulins (Ig) are recognized in animals. IgM is the largest, forming up to 15% of the total immunoglobulin present. IgM exists as a monomer or a large polymeric form. IgM is responsible for the primary immunoglobulin response; in animals, for some infections it is the only defense (Gorman, 1995). The availability of five binding sites renders IgM efficient at antigen binding and agglutination, virus neutralization, and opsonization. IgM also is a potent activator of complement. Because it is such a large molecule, unless vascular permeability is altered, most IgM stays in circulation.

IgG (with multiple subclasses) makes up the majority of total Ig. It is the most soluble of the immunoglobulins and thus is able to reach extravascular spaces. Its primary biologic functions are to facilitate the removal of microorganisms, neutralize toxins, and bind to microorganisms or infected cells, initiating effector mechanisms. IgG activates complement or initiates Fc-bearing effector cells (ADCC) and promotes removal of immunoglobulin-coated cells by ADCC.

IgE has a major role in the response to parasites and in the pathogenesis of allergic diseases in part because of its unique ability to bind via the Fc portion of the IgE molecule to specific receptors on mast cells and basophils. Cross-linkage of two IgE molecules results in calcium-mediated mast cell degranulation and the release of a number of preformed (e.g., histamine and serotonin) and synthesized (e.g., metabolites of arachidonic acid) mediators.

IgA is produced in submucosal lymphoid tissues and regional lymph nodes. After secretion outside of the cell, it travels to epithelial cells, where the secretory component of the IgA acts as a receptor, binding to IgA and stimulating its endocytosis. The two components are eventually exocytosed and attach to the mucosal surface, where they provide a protective component, neutralize toxins, adhere to bacteria and viruses, and interact with parasites (Gorman, 1995).

Each immunogloblin molecule monomer is comprised of two heavy chains and two light chains attached by covalent bonds. The number of bonds varies with the immunoglobulin; the number of dimers varies with the class. A number of fragments (generated by enzymatic cleavage) can be described: Fab, the antigen-combining fragment; and Fc, the crystallizable fragment (Gorman, 1995).

Hypersensitivity Reactions

Four types of reactions result from activation of immunologic pathways. Type I hypersensitivity results from antigen-IgE interaction (Fig. 19–2). IgE that has previously interacted with the antigen binds to the surface of a basophil or mast cell. Subsequent interaction with the same antigen causes mast cell degranulation and the release of a number of mediators associated with *immediate hypersensitivity.* The reaction associated with mediator release can be instantaneous (e.g., anaphylaxis), delayed for 2 to 4 hours, or biphasic with both an immediate and a delayed reaction. Systemic release of mediator results in systemic anaphylaxis; localized mediator release limits reaction to the site of release. Atopy is an inherited predisposition to develop IgE antibodies to environmental antigens, and is characterized by constant high levels of IgE. Occasionally, non-immune-mediated mast cell degranulation can occur (e.g., cationic drug-induced), resulting in an anaphylactoid reaction.

Type II hypersensitivity occurs when ADCC occurs after antibody binds to a cell or to an exogenous antigen associated with a cell surface or a basement membrane. Complement may be activated and contribute to the damage. Examples of type II hypersensitivity include drug hypersensitivities, autoimmune hemolytic anemia, immune-mediated thrombocytopenia, immune-mediated endocri-

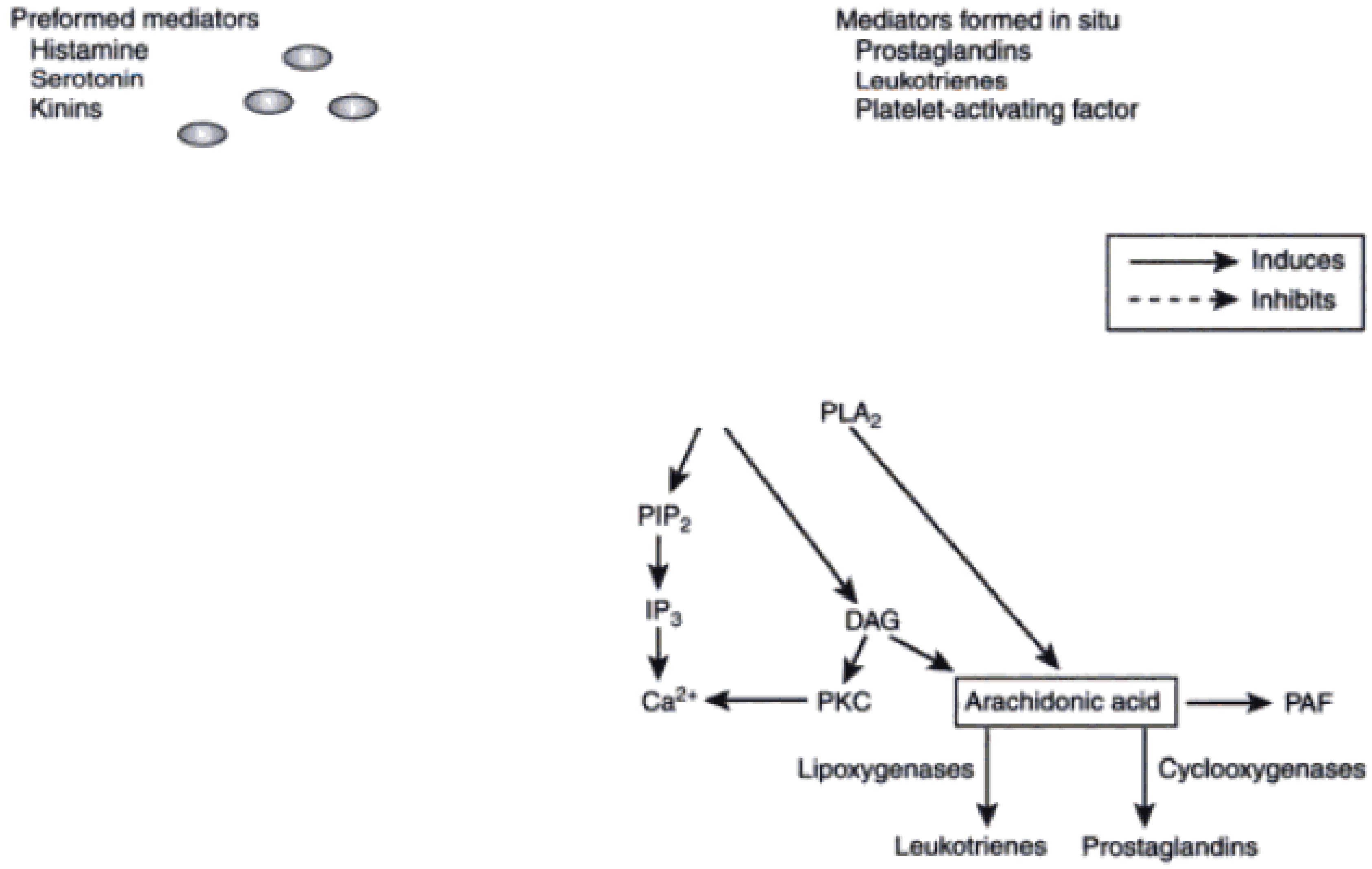

Figure 19–2. Diagrammatic representation of a type I hypersensitivity reaction involving antigen bound to IgE and calcium-mediated degranulation. Degranulation results in the release of both preformed mediators and mediators formed in situ (e.g., from arachidonic acid). Stimulation of muscarinic (M_3) receptors supports exocytosis, which is inhibited by stimulation of β_2-adrenergic receptors. cAMP = cyclic adenosine monophosphate; cGAMP = cyclic guanosine monophosphate; DAG = diacylglycerol; IP_3 = inositol triphosphate; PAF = platelet-aggregating factor; PDE = phosphodiesterase; PIP_2 = phosphatidylinositol; PKC = protein kinase C; PLA_2 = phospholipase A_2; PLC = phospholipase C.

nopathies, and immune-mediated dermatologic disorders such as bullous pemphigus (Gorman, 1995).

Type III hypersensitivity results from the formation of antigen-antibody or immune complexes that either circulate or are deposited as microprecipitates in vascular beds or basement membranes. The Arthus reaction occurs 2 to 4 hours after IgG interacts with an antigen in the vessel wall. Serum sickness occurs when circulating immune complexes develop as a result of intravascular injection of the antigen. Microprecipitates in circulation deposit in basement membranes and the vascular endothelium, resulting in immune complex diseases. The risk of serum sickness increases with the persistence of antigen. The size of the immune complex also determines the degree of damage because larger complexes are more likely to deposit and initiate inflammation. Complement both contributes to and protects against damage caused by immune complex disease (Gorman, 1995).

Type IV hypersensitivity involves sensitized T cells that initiate a cell-mediated reaction on interaction with the appropriate class II MHC antigen. Lymphocyte and macrophage influx to the site occurs over a 24- to 72-hour period. Allergic contact dermatitis is an example of a type IV hypersensitivity (Gorman, 1995).

Immunomodulatory Effects of Opioids

The possibility of opioid influence on the immune system was first recognized close to 100 years ago based on the effects of opium on phagocytic function (Mellon and Bayer, 1998). Additionally, people addicted to heroin are more susceptible to infection. Rodent studies indicate increased mortality and morbidity when opioid-treated animals are exposed to infectious agents. The presence of opioid receptors on cells of the immune system has been recognized since the late 1970s (Carr et al., 1996; Mellon and Bayer, 1998). Although further studies are needed to fully elucidate the effect of opioids on immune function, thus far both the cellular and humoral immune reactions are impacted.

Effects are variable but are directed centrally rather than peripherally and involve primarily but not exclusively supraspinal mu receptors. Effects (inhibitory vs. stimulatory) are dose dependent but occur at clinically relevant doses in animal models. Multiple central opioid receptors as well as endogenous opioids appear to be involved in complex immune responses. Natural killer cytolytic activity and mitogen-stimulated T-cell proliferation are reduced by centrally administered morphine via mu receptors, whereas antibody production is both increased and decreased by met-enkephalin, probably reflecting interaction with multiple receptors. Effects can occur with single or multiple administration of exogenous opioids. Both the neuroendocrine system and the autonomic nervous system may serve as the efferent mechanisms mediating central opioid modulation of the immune system (Mellon and Bayer, 1998). Tolerance appears to develop to some of the immunomodulatory effects, but this remains controversial. The clinical implications regarding the role of opioids in modulating the immune response are not clear.

CLASSIFICATION OF IMMUNOMODULATORY DRUGS

Immunomodulators often are classified according to their source: microbial, animal, or synthetic. Immunomodulators can also be classified by their effect on the immune system: they either enhance or inhibit the immune response. "Pro-host" agents augment the cellular immune response either by facilitating a normal response (immunorestoratives) or by stimulating the immune response (immunostimulants). Immunostimulants can be used either before antigenic challenge to protect immunocompromised patients at risk or animals exposed to virulent agents or after exposure has occurred to promote immune function. Immunosuppressant agents are used to manage hypersensitivity reactions, including autoimmune diseases, and as anticancer drugs. Many immunomodulatory drugs are target specific in their effects. Many also, however, have nonspecific effects that affect several to many arms of the immune response. Immunostimulants may in fact inhibit components of the immune response in some instances. Care should be taken when selecting an immunomodualtory drug, particularly if all the effects of the drug are not known or anticipated. For example, selective depression of some virally induced immune reactions are beneficial if the host immune response to the infecting virus threatens the host's survival. Drugs that inhibit B-lymphocyte activity (e.g., cyclophosphamide) often lower the mortality associated with some human influenza viruses and presumably should prove beneficial for the treatment of feline viral diseases associated with poorly controlled immunoglobulin production (i.e., feline infectious peritonitis).

The major indications for pharmacologic modulation of the immune system in animals are treatment of autoimmune diseases; prevention or treatment of infections, particularly in immunocompromised hosts; and prevention and therapy of malignancies. A less common but increasingly growing use of immunomodulators in small animals is treatment of graft-versus-host reactions after organ transplantation.

IMMUNOMODULATION IN VIRAL AND NEOPLASTIC DISEASES

Viral Diseases

Biologic response modifiers potentially offer a logical and unique approach to the treatment of viral diseases because (1) viruses are capable of immunosuppression and (2) the immune response is an important determinant in the host's ability to overcome viral infection (Ford, 1986; Carrasco, 1984). Resistance against and recovery from viral infections in mammals depend on three components of the immune system. The mononuclear phagocytic (reticuloendothelial) system represents the first barrier to viral infections, but it is nonspecific and not always efficient. Sensitized T lymphocytes provide specific cell-mediated immunity, which is followed later by humoral events, either narrowly specific (antibodies) or nonspecific (interferon). There are multiple interactions between these systems. Unfortunately, several of these systems also contribute to the pathogenesis of viral disease. Viruses may cause immunosuppression by several mechanisms: they may directly injure or impair all classes of lymphocytes, cause the production of soluble immunosuppressing chemicals (e.g., interferon, p15[E] of feline leukemia virus), damage all three cell systems by infection, or cause an imbalance in immunoregulation, thus leading to overactivity of suppressor T cells.

Neoplastic Diseases

Many tumors have surface antigens toward which specific antibodies can be directed. Biologic response modifiers can alter response to tumor antigen at one or several of these points, depending on the drug. Some biologic response modifiers augment or restore normal host effector mechanisms by acting as either a mediator or an effector of the antitumor response. Transformation of tumor cells may be decreased or maturation of tumor cells may be increased by biologic response modifiers. Host tolerance of damage caused by cytotoxic chemotherapeutic drugs also may be increased by biologic response modifiers. Finally, biologic response modifiers have been used to alter patient response to feline leukemia virus viremia and thus the subsequent associated neoplasms (MacEwen, 1985; Theilen and Hills, 1982).

BIOLOGIC RESPONSE–MODIFYING DRUGS

The sequelae of immunomodulation are not always beneficial; alteration of the immune response can impair many aspects of the host's normal defense system. The use of immunomodulators is still in the preliminary stages, and this is particularly true for veterinary medical applications (Table 19–2). Because of the many facets of the immune system susceptible to regulation, the dose, timing, and route

Table 19–2. Dosing Regimens of Immunomodulating Drugs

Drug	Dose	Route	Interval
Acemannan	2 mg	Intratumorally	Weekly for 6 weeks
	1 mg/kg	Intraperitoneally	Weekly for 6 weeks
Aurothioglucose			
Test dose	1 mg < than 10 kg, 5 mg ≥ 10 kg	IM	Twice, 1 week apart
	1 mg/kg (D)	IM	weekly until remission; then alternate weeks
With prednisolone	1–2 mg/kg	PO	12-48 h
	0.5–1.0 mg/kg (C)	IM	7 days
Auranofin	0.1–0.2 mg/kg	PO	12 h
Azathioprine	2 mg/kg	PO	24 h
With prednisolone	1 mg/kg	PO	12 h
Chlorambucil	0.1–0.2 mg/kg	PO	48 h
Cyclophosphamide	100–250 mg/m^2	IV bolus	Once
	50 mg/m^2	PO	48 h
With prednisolone	1 mg/kg	PO	12 h
Cyclosporine	4–6 mg/kg	IV infusion over 4 h	
Perianal fistulas	5–10 mg/kg	PO	12 h
Renal allografts	7.5 mg/kg	PO	12 h
With prednisolone	0.125–0.25 mg/kg	PO	12 h
Danazol	2–5 mg/kg	PO	24 h
Dexamethasone	0.1–0.2 mg/kg	IV	
Dimercaprol	4 mg/kg	IM	4 h
Fibronectin	0.5–2.0 mg/kg	IV	24 h
Human gammaglobulin	0.5–1.5 g/kg	IV infusion	Over 12 h
Levamisole	2.5–5 mg/kg	PO	Three times weekly
Megestrol acetate			
Induction	2.5–5 mg/cat	PO	48 h, every other day
Maintenance	2.5 mg/cat	PO	7–14 days
Methylprednisolone acetate	2 mg/kg, minimum of 20 mg	Intralesional	14 days
Niacin	5–12 mg/kg	PO	8 h
Pentoxifylline	30 mg/kg (D)	PO	8–12 h
Prednisolone, prednisone			
Immunosuppressive	1–3 mg/kg	IV, SC, PO	12 h
Alternate-day target	0.25–0.5 mg/kg	IV, SC, PO	48 h
Promodulin	50 mg/kg up to 200 mg	IV	24 × 5
Tetracycline	5–12 mg/kg	PO	8 h
Vitamin E acetate or succinate	400 IU	PO	12 h; 2 h before or after a meal
Vinblastine	0.1–0.4 mg/kg	IV	7–14 days
	2 mg/m^2 (C)	IV	7–14 days
	1–3 mg/m^2 (D)	IV	7 days (in a protocol)
Vincristine	0.010–0.025 mg/kg (D)	IV	7–10 days
Immune-mediated thrombocytopenia			
Neoplasia	0.5–0.75 mg/m^2	IV	7–14 days

Abbreviations: C, cat; D, dog; IM, intramuscular; IV, intravenous; PO, oral; SC, subcutaneous.

of administration of these drugs are important to avoiding undesired affects. In addition, host effects such as age and nutritional status and the nature of the disease may be important determinants in the patient's response to these drugs.

Immunosuppressant Drugs

Several principles should guide use of immunosuppressant drugs (Diasio and LoBuglio, 1995). First, suppression of the primary immune response is more easily accomplished than is suppression of the secondary (amnestic) response. Second, successful inhibition or suppression is easier if therapy begins before exposure to the inciting immunogen (antigen). Third, immunosuppressive drugs do not cause the same effect on all aspects of the immune system. Often, opposite effects are concentration dependent. Thus, failure to achieve the desired response should not necessarily lead to an increase in dose.

Two major limitations characterize immunosuppressive therapy. Patients receiving immunosuppressive therapy are predisposed to infections of any type. In addition, the risk of lymphomas and related malignancies is increased. This latter risk is more problematic in human patients because, in part, of their longer life span. Events that immunosuppressive drugs tend to target include antigen recognition, stimulation of IL-1, synthesis and release of IL-2 or other cytokines, and lymphocyte proliferation and differentiation (Diasio and LoBuglio, 1995). Secondary signal molecules are also becoming increasingly important as targets of immunosuppressive therapy.

The primary indication for the use of immunosuppressant drugs in veterinary medicine is treatment of autoimmune disorders. Such disorders are characterized by sensitization to endogenous proteins that are perceived to be foreign. Both cell-mediated and humoral responses can be directed toward the protein. Many immune-mediated disorders afflicting dogs and cats respond sufficiently well to glucocorticoids (discussed in Chapter 17) and, when necessary (in severe cases), cytotoxic drugs. These include immune-mediated autoimmune hemolytic anemia or thrombocytopenia, acute glomerulopathies, and many dermatologic disorders with an immune-mediated basis.

Cyclosporin A

Chemistry-Structure Relationship

Cyclosporin A (CsA), now known as cyclosporine, is the most important immunosuppressive drug for human transplantation and the treatment of selective autoimmune disorders (Diasio and LoBuglio, 1995). Cyclosporin A is one of nine cyclosporins (A through I), each a cyclic peptide drug (Fig. 19–3) isolated from the fungi *Cyclindrocarpon lucidium* and *Trichoderma polysporum*. The drug is very lipophilic and very hydrophobic and must be solubilized before administration (Diasio and LoBuglio, 1995). The intravenous (IV) preparation is an ethanol–polyoxyethylated castor oil mixture. The oral preparation is a soft gelatin capsule (Sandimmune) or a (newer) microemulsion formulation (Neoral). Historically, CsA has been formulated in peanut oil (for treatment of ophthalmic ocular disorders in dogs); however, an approved product formulated for topical use is now available.

Mechanism of Action

Cyclosporine is a unique immunosuppressant in that it specifically inhibits Th cells early in their immune response to antigenic and regulatory stimuli (Diasio and LoBuglio, 1995) without affecting suppressor cells. Suppression occurs as CsA binds to cyclophilin, a cytoplasmic receptor protein, forming a heterodimeric complex. This complex then binds to calcineurin. Binding of calcineurin inhibits calcium-stimulated phosphatase activity that results in dephosphorylation of regulatory proteins. Dephosphorylation of the proteins causes their translocation to the nucleus, where they serve as subunits of transcription factor complexes. Thus, CsA prevents the enhanced transcription of

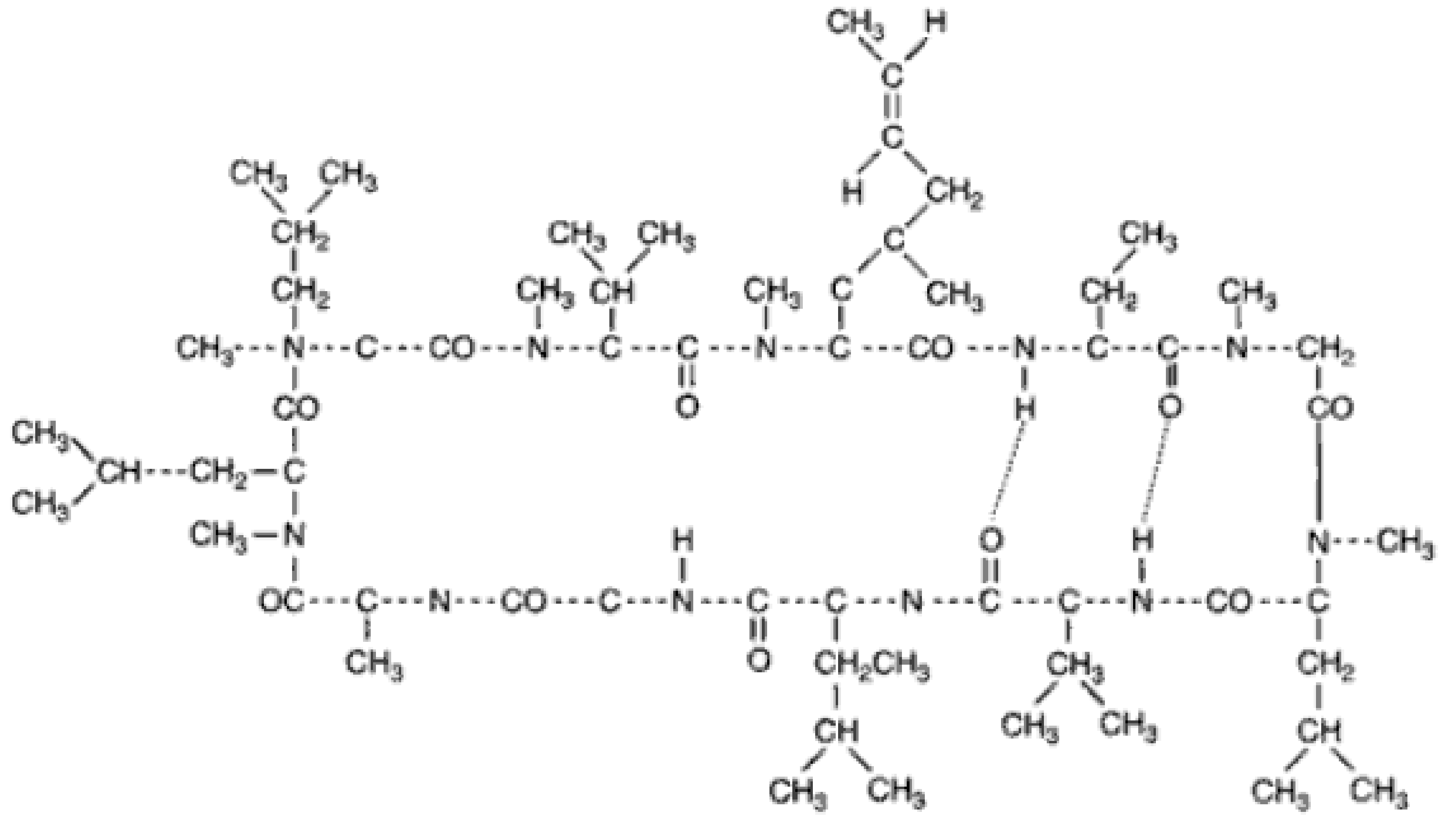

Figure 19–3. The chemical structure of cyclosporine.

T-cell genes that would otherwise occur after T-cell activation. Transcription mediated by IL-2, certain protooncogenes, and selected cytokine receptors are particularly affected (Diasio and LoBuglio, 1995). Interleukin-2 production (and thus T-cell proliferation and antigen-specific cytotoxic T-lymphocyte generation) also is attenuated because the expression of transforming growth factor, a potent inhibitor of IL-2, is increased (Diasio and LoBuglio, 1995). B cells are not affected. The drug is most effective when administered before T-cell proliferation has occurred.

Clinical Pharmacology

The pharmacokinetic behavior of CsA is complex and apparently has not been studied in dogs or cats. Absorption after oral administration is slow and incomplete. In humans, oral bioavailability of the capsule ranges from 20 to 50% but is improved by 10 to 20% in the microemulsion form (Diasio and LoBuglio, 1995; Friman and Backman, 1996). In contrast to earlier preparations, the oral absorption of the microemulsion is not dependent on bile acids (Friman and Backman, 1996). Peak concentrations occur 1 to 4 hours after oral administration in human beings. When the capsule—but not the microemulsion—is administered with a fatty meal, absorption is slowed. Studies suggest that decreased bioavailability of CsA after oral administration may reflect activity of drug-metabolizing enzymes of the intestinal epithelium (Gomez et al., 1995) or P-glycoprotein–mediated drug efflux.

Cyclosoporine is widely distributed, characterized by a large volume of distribution (13 L/kg in humans). The drug accumulates in erythrocytes (accounting for 50% or more of the drug in humans), and leukocytes (accounting for 10 to 20% of circulating drug in humans) (Diasio and LoBuglio, 1995). Remaining circulating drug is bound to plasma lipoproteins. The drug is metabolized by the liver to a large number of metabolites, which are likely to vary among animals. Over 20 metabolites have been documented in humans. Metabolism is targeted primarily toward the side chains rather than the ring structure. Metabolism appears to totally inactivate the drug, although this has not been shown conclusively (Diasio and LoBuglio, 1995). Metabolites are excreted in bile and feces. The elimination half-life of CsA in humans is 6 hours.

Drug Interactions

The risk of drug interactions is another indication of the need for therapeutic drug monitoring as a guide to proper dosing regimens. A number of interactions between CsA and other drugs have been reported in the human literature (Diasio and LoBuglio, 1995). Its elimination is accelerated, probably in part due to induction of drug-metabolizing enzymes, by phenytoin, phenobarbital, rifampin, and sulfamethoxazole/trimethoprim combinations. Its elimination is decreased by amphotericin B, erythromycin, and ketoconazole (Diasio and LoBuglio, 1995). Cyclosporine also appears to alter the oral absorption of other drugs (Gomez et al., 1995). As an inhibitor of P glycoprotein, cyclosporine can increase the oral bioavailability of drugs that otherwise would be effluxed from intestinal epithelials cells into the intestinal lumen (Terao et al., 1996). Cyclosporine can be used with other immunosuppressive drugs, including glucocorticoids (Diasio and LoBuglio, 1995).

The inhibitory effect of ketoconazole on intestinal epithelial and hepatic drug metabolism may be of therapeutic benefit in patients receiving cyclosporine. Administration of drugs (e.g., ketoconazole) known to inhibit the metabolism of CsA (potentially targeting intestinal epithelials cells as well as hepatic microsomal enzymes) not only decreases the hepatic clearance but also increases the bioavailability of the drug (Gomez et al., 1995; McLachlan and Tett, 1998). Ketoconazole may also decrease the lipoprotein that binds cyclosporine, resulting in higher concentrations of free cyclosporine (Keogh et al., 1995). Differences in oral bioavailability of cyclosporine among animals also may reflect the presence of intestinal P glycoprotein, a protein responsible for the efflux of drug from cells. P glycoprotein appears to contribute to first-pass elimination of cyclosporine by acting as a rate-limiting step in absorption (Lown et al., 1997).

The use of ketoconazole in conjunction with cyclosporine as a means of decreasing drug costs apparently has been well accepted in human medicine (Keogh et al., 1995) but is supported by therapeutic drug monitoring. The two drugs have been used safely for up to 47 months in one study (Keogh et al., 1995). The dose of cyclosporine has been reduced as much as 88%. The effects occur rapidly: 62% of the effect is apparent by day 7 in humans, although the maximum inhibitory effect may not be present for 12 months. Interestingly, the combination drugs resulted in a lower rejection rate than did cyclosporine alone (Keogh et al., 1995). The effect of combining ketoconazole with cyclosporine has been studied in dogs (Myre et al., 1991). Ketoconazole was studied at doses ranging from 1.2 5 to 10 mg/kg per day, with the magnitude of inhibition increasing with the dose of ketoconazole. Inhibition of clearance occurred at doses less than 2.5 mg/kg per day; clearance was reduced by 85% at 10 mg/kg per day. Differences in clearance did not, however, appear to affect bioavailability. Other drugs that decrease clearance of cyclosporine include diltiazem, verapamil, and itraconazole (McLachlan and Tett, 1998). The impact of cimetidine or chloramphenicol, both inhibitors of hepatic drug–metabolizing enzymes, appears to have not been reported.

Side Effects

Cyclosporine is characterized by a narrow therapeutic index in human patients, with renal toxicity the primary adverse effect. Renal tubular cells develop hyperuricemia (worsened by diuretics) and hyperkalemia (a renal tubular and erythrocyte ion channel effect) (Kahan, 1993). Hepatic injury also occurs. Although less common than renal dysfunction, the risk of severe hepatic damage is markedly increased when cyclosporine is used in combination with cytotoxic drugs. Cyclosporine also increases the incidence of gallstones in human patients. The risk of renal and hepatic toxicities does not appear to be as great in small animals. The risk of renal damage is, however, likely to be enhanced with concurrent administration of several other drugs, including other nephrotoxic drugs, and may be of greater risk in animals undergoing renal transplantation.

Hyperlipidemia also has been reported in humans, particularly in patients receiving glucocorticoids. Other side effects reported in humans include hepatotoxicity, neurotoxicity, gastrointestinal upset, and hypertension (Diasio and LoBuglio, 1995). Development of B-cell lymphoma also has been reported. The commercial form intended for IV use has been associated with anaphylactoid reactions in the dog due to the solubilizing agent.

Cyclosporine concentrations should be monitored as a guide to effective yet safe dosing regimens. Guidelines offered in human medicine have served as targets for veterinary patients (Kahan, 1993). Several methods are available for measuring cyclosporine concentrations, including high-performance liquid chromatography (HPLC), which can separate metabolites from the parent drug, and immunoassays based on radioimmunoassays (RIA) and polarized immunofluorescence, which is likely to detect parent drug and metabolites. Each appears to be clinically useful, although the target concentrations will vary with the methodology. Samples may vary, with whole blood being the most common. The laboratory to be used should be contacted before sample collection. Plasma or blood concentration of cyclosporine is the predominant determinant of drug effect (Kahan, 1993), although an active metabolite may contribute up to 10% of activity in humans not receiving ketoconazole.

Serial pharmacokinetic profiling has been recommended in lieu of single trough concentrations because the latter do not correlate to area under the concentration curve (Kahan, 1993). Variability in disposition (ninefold variation in drug absorption and sixfold in clearance) also necessitates serial sampling in persons receiving the drug. With polarized immunofluorescent methods of detection, a steady-state concentration of 400 ± 40 ng/mL is targeted with this methodology in people undergoing transplantation. Unfortunately, development of a full pharmacokinetic profile (including clearance) requires IV administration of the drug (a route used after renal transplantation), a route not used in animals. Collection of a peak and a trough sample can be used to generate an area under the curve (most easily implemented with computer software); when divided by the dosing interval, concentrations should approach 550 to 600 ng/mL. Trough concentrations should remain above 200 ng/mL in order to be immunosuppressive. In human patients undergoing transplantation, establishing the pharmacokinetics of the drug before transplantation appears to be very useful to determine the proper post-transplantation dose (Kahan, 1993). Although therapeutic drug monitoring can be used to guide dosing regimens such that efficacy and safety are enhanced, laboratories offering cyclosporine assays are limited, and the assays can be expensive.

Therapeutic Use

In veterinary medicine, the major indication for cyclosporine (as a topical treatment) has been keratitis sicca (Williams, 1997). Benefits include both immunomodulation and an increase in tear production. A 0.2% cyclosporine compound in a petrolatum–corn oil ointment is commercially available (Schering Plough) for keratitis sicca in dogs. A homemade preparation of 2% cyclosporine in corn oil was used before the commercial preparation (2 mL cyclosporine added to 10 mL of corn oil) became available. Application of one drop of the commercial preparation twice daily should be effective in up to 80% of dogs. The frequency of administration can be decreased to every other day for most dogs.

Cyclosporine has been used systemically for a number of disorders. Because cats may find the oral preparation unpalatable, the oral solution can be given diluted in olive oil. The IV preparation (4 to 6 mg/kg as a 4-hour IV infusion) can be given to animals for which oral administration is not possible (Vaden, 1995). The vehicle of the IV preparation is very irritating and must not extravasate. Monitoring is recommended at least monthly for the first several months of therapy and preferably weekly for the first month of therapy, or until concentrations are stable. Concentrations may vary with the methodology of detection and the tissue sampled. For example, monitoring of whole blood (WB) versus plasma or serum (PS) (based on human data) should yield the following trough concentrations (ng/ml): for HPLC, 100 to 300 (WB); RIA, monoclonal antibody methodology: 150 to 400 (WB) or 50 to 125 (PS); RIA, polyclonal antibody methodology: 200 to 800; fluorescent polarized immunoassay: 250 to 1000. Values have been reported for cats and dogs for selected assays (Vaden, 1995), but it is not clear if these ranges reflect therapeutic ranges or concentrations achieved after selected dosing regimens.

A recent indication for cyclosporine treatment in dogs is perianal fistulas. Mathews and coworkers (1997) found that cyclosporine was effective in eradicating or markedly reducing the size or number of perianal fistulas in 10 of 10 dogs. Initial dosing began at 10 mg/kg orally every 12 hours but was reduced to 5.0 to 7.5 mg/kg after 1 week because of excessive trough concentrations. Doses were adjusted to a trough measurement of 400 to 600 ng/mL. Duration of therapy ranged from 8 to 12 weeks; remission required another 4- to 6-week trial of therapy in 3 dogs. Remission was persistent in all dogs for at least 6 months and up to 18 months at the time the report was published. A follow-up study of a randomized controlled trial in 20 dogs (Mathews and Sukhiani, 1997) found that fistulas recurred in 7 of 17 dogs treated with cyclosporine and required subsequent treatment or surgical excision. Cyclosporine was, however, beneficial presurgically to reduce the extent of excision. The investigators also found that trough cyclosporine concentrations between 100 and 300 ng/mL were effective for treatment of perianal fistulas. The most frequently reported side effect in this study was shedding of hair, noticeable by 16 weeks. Older hair coats tended to be replaced with a softer coat.

A cost analysis reveals the use of ketoconazole to be economically sound for reducing the dose of cyclosporine. For a 40-kg dog, 7.5 to 15 mg/kg per day of cyclosporine costs $15.00 to $30.00 per day. If ketoconazole is added at 2.2 to 8.5 mg/kg, the dose of cyclosporine can be reduced to 1.0 to 3.5 mg/kg. With the combination of ketoconazole and cyclosporine, the lowest cost would be $6.20 per day (2.2 mg/kg ketoconazole and 1.0 mg/kg cyclosporine) and the highest cost would be $19.00 per day (8.5 mg/kg ketaconazole per day and 3.5 mg/kg cyclosporine per day). This is based on a cost of cyclosporine (Neoral) of $2.00 per 25-mg capsule and $4.36 for a 200-mg capsule of ketoconazole. Note, however, that the proper dose of ketoconazole is not known; it might be recommended to start in the middle of the dosing range for the both drugs. We have used ketoconazole at a dose of 7 mg/kg twice daily and cyclosporine at 3.5 mg/kg per day. Within 1 week, trough cyclosporine concentrations were 1000 ng/mL. The dose of cyclosporine was decreased by 50%; trough concentrations 1 week after the dose decrease were 540 ng/mL. The interval for cyclosporine was subsequently prolonged to 48 hours. Cyclosporine should be monitored at weekly intervals for the first week and then biweekly as needed. Both a peak and a trough sample would be ideal; a trough sample is recommended if only one sample can be collected.

Cyclosporine also is being used increasingly for patients suffering from autoimmune disorders that have not responded to traditional immunosuppressive therapy. I and others have used cyclosporine successfully for treatment of pure red cell aplasia (Barth et al., 1997). A randomized placebo-controlled study on the use of cyclosporine for treatment of spontaneous glomerulonephritis in dogs (Vaden, 1995) found no differences between treatment groups in improvement. Packed cell volume was lower in the cyclosporine-treated group; in addition, clinical signs compatible with decreasing renal function appeared to be more severe in animals receiving cyclosporine. Cyclosporine appears to act synergistically with dexamethasone for the treatment of inflammatory bowel disease in human patients. Each drug appears to target through different mechanisms the chemokines responsible for migration of white blood cells to the site of inflammation (van Deventer 1997). Cyclosporine does not appear to be effective for the treatment of immune-mediated glomerular nephritis in dogs (Vaden, 1995).

With the advent of renal transplantation availaoility at several facilities, CsA is increasingly being used to prevent graft-host rejections. Cats respond better than dogs, with renal allografts being maintained at 7.5 mg/kg every 12 hours coupled with prednisolone (0.125 to 0.25 mg/kg every 12 hours) (Vaden, 1995). Trough concentrations of whole blood should be maintained at 500 ng/mL (HPLC) the first month after transplantation but can be reduced to 250 ng/mL thereafter.

Other potential indications for cyclosporine warrant further investigation. Cats suffering from *Ascaris suum*–induced airway reactivity had decreased reactivity and remodeling after receiving cyclosporine; differences were noted with 24 hours of therapy (Padrid et al., 1996). Cyclosporine therapy was successful in treating aplastic anemia in three of four dogs (Barth et al., 1997) when dosed at 5 to 10 mg/kg every 12 hours. Cyclosporine may have applications in dermatologic diseases. When compared with dexamethasone and indomethacin, topical cyclosporine was equal in suppressing arachidonic acid-induced inflammation (Puignero and Queralt, 1997), and studies are under way to evaluate its use in canine dermatologic diseases.

Tacrolimus

Tacrolimus is another macrolide antibiotic produced by *Streptomyces*. Like cyclosporine, it inhibits T-cell activation by binding to a cytosolic protein and ultimately inhibiting calcineurin-dependent activation of lymphokine expression, apoptosis, and degranulation (Diasio and LoBuglio, 1995). The intracellular receptors for tacrolimus are distinct from those for cyclosporine. The drug is available for both oral and intravenous administration. Toxicities are similar to those of cyclosporine in people. The drug may be more toxic than cyclosporine in dogs, and its use has not been recommended (Vaden, 1997).

Mycophenolate Mofetil

Mycophenolate mofetil (MMF) is the morpholinoethyl ester pro-drug of mycophenolic acid (MPA), a potent, selective, reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH). This enzyme is critical for the production of the guanine triphosphate precursor guanine monophosphate, which in turn is necessary for the de novo synthesis of purine nucleotides. As such, the drug is an antimetabolite. Unlike other anticancer antimetabolites, MMF and its active metabolite MPA are relatively selective for lymphocytes because they are solely dependent on de novo synthesis of purines for DNA synthesis (Langman et al., 1996; Pirsch and Sollinger, 1996). The drug is the first to be approved in the United States since cyclosporine for prevention of renal allograft rejection.

The primary side effects in human patients receiving the drug for allograft rejection are leukopenia, gastrointestinal upset, and cytomegalovirus disease. The incidence is, however, small. A bilateral nephrectomized dog model has been used to study this drug, and pharmacokinetic data gathered after oral absorption are available (Langman et al., 1996). The disposition appears to be characterized by marked variability. After doses of either 20 or 40 mg/kg, mean peak concentrations of MPA are, respectively, approximately 90 and 130 mg/L, although peak concentrations did not statistically differ between the two groups. Based on lymphocytes exposed to whole blood containing MPA, 200 mg/L MPA is necessary to inhibit baseline activity of IMPDH by 50%. The elimination half-life of the drug ranges from 1.45 to 11.09 hours, with a mean of approximately 7 hours, regardless of the dose. Based on these data, a dose of 20 mg/kg every 8 hours was chosen for a study of dogs with myasthenia gravis. The drug appears to be relatively safe based on renal and hepatic indices of damage even when dosed at 80 mg/kg twice daily. At that dose, transient elevations of hepatic damage enzymes can be expected (Platz et al., 1991). The drug currently is under investigation for application in canine immune-mediated disorders.

Leflunomide

Leflunomide is an experimental drug that inhibits de novo synthesis of pyrimidine. It is being studied for the treatment of rheumatoid arthritis in humans (Smolen et al., 1999). Like MMF, it is a pro-drug. Unlike MMF, however, little information appears to be available regarding its use in dogs (Gregory et al., 1999). Anecdotal reports suggest that the drug is effective for treating canine cutaneous histiocytosis and pemphigus foliaceus (2 to 4 mg/kg orally every 24 hours). Side effects that reportedly occur in dogs include leukopenia, thrombocytopenia, and gastric ulceration.

Hormones

Glucocorticosteroids (see Chapter 17) possess both anti-inflammatory and immunomodulatory capabilities. Immunomodulation results in actions at a variety of targets in the acquired immunodeficiency syndrome (see Chapter 20). Selected progestational compounds (e.g., megestrol acetate) have been used for their general immunosuppressive effects. Megestrol acetate may have longer and more potent anti-inflammatory effects compared with glucocorticoids (Rhodes et al., 1995); however, in the cat, the species for which these products tend to be used, side effects can be dramatic and life threatening. Thus, their use is recommended only for conditions that will not or have not responded to glucocorticoids.

Danazol is classified as an androgen but is characterized by weak androgenic activity. In human patients, danazol has proved effective in stimulating increased concentrations of complement inhibitor and thus is indicated for treatment of angioneurotic edema (Wilson, 1995). Danazol also has immunomodulatory effects that are of benefit in type II immune complex diseases. Danazol apparently decreases the expression of or blocks Fc receptors on macrophages (Ward, 1995; Stadtmauer et al., 1991; Choudhry et al., 1995; Schreiber et al., 1987). The drug has proved useful in a number of type II immune-mediated diseases, including immune-mediated hemolytic anemia (autoimmune hemolytic anemia) and immune-mediated thrombocytopenia (Gorman, 1995; Ward, 1996; Bloom et al., 1989; Holloway et al., 1990).

Cytotoxic Drugs: Antimetabolites and Other Antineoplastic Agents

Antimetabolite and alkylating antineoplastic agents (see Chapter 18) are also used as chemical immunosuppressants by virtue of their effects on actively dividing cells (Langford et al., 1998a, b). Their effects should, however, be regarded as nonspecific. Macrophages, activated T and B cells, and natural killer cells are the targets of most of the drugs. Those most commonly used for their immunomodulatory effects are cyclophosphamide and azathioprine. In general, neither drug is sufficiently immunomodulatory and safe to allow use as the sole agent.

Cyclophosphamide is a nitrogen mustard. Its immunomodulatory effects reflect the same mechanism of action as its anticancer effects (see Chapter 18). Cyclophosphamide alkylates DNA in both proliferating and nonproliferating cells; proliferating cells are more susceptible to alkylation. Both B and T cells are impaired. Because B cells recover more slowly, however, cyclophosphamide inhibits the humoral response more than the cell-mediated response (Diasio and LoBuglio, 1995). Note that at very high doses cyclophosphamide can actually induce tolerance to an antigen to which the patient has been exposed. Toxicities of cyclophosphamide are typical of drugs that target proliferating cells. In addition, hemorrhagic cystitis has been reported in dogs receiving the drug (see Chapter 18). Cyclophosphamide therapy should be discontinued if the neutrophil or platelet counts decreased less than 2000/μL or less than 100,000/μL, respectively. Azathioprine interacts with nucleophils to form 6-mercaptopurine, which is converted to nucleotides. The nucleotides interfere with purine synthesis or cause DNA damage. The drug is available for both oral and intravenous administration. Coadministration with allopurinol increases the risk of toxicity. Toxicity results from inhibited growth of rapidly growing cells, including cells of the bone marrow and gastrointestinal tract. Although azathioprine has been used in the cat, reformulation may be necessary for accurate dosing.

Chlorambucil is also a nitrogen mustard, and its cytotoxic effects are similar to those of cyclophosphamide. The drug is available in an oral preparation that allows accurate dosing in cats (Rhodes, 1995). In contrast to cyclophosphamide, chlorambucil's myelosuppression is only moderate and gradual. Toxicities are rare in cats (Rhodes, 1995). The incidence of gastrointestinal side effects can be reduced by alternate-day dosing. In human patients, however, excessive doses can cause hypoplastic bone marrow. Its effects (e.g., in chronic lymphocytic leukemia) are gradual in onset (Chabner et al., 1995). Therapeutic indications in the cat include pemphigus foliaceus and refractory cases of feline granuloma complex.

Vincristine is used to treat immune-mediated thrombocytopenia because of its ability to cause the maturation and release of mature thrombocytes from the bone marrow by stimulation of megakaryocyte endomitosis. Other anticancer drugs used for immunomodulatory effects include methotrexate, chlorambucil, and vinblastine. The nonspecific effects of anticancer drugs on the immune system and other rapidly dividing cells limits their use due to host toxicity (primarily bone marrow and gastrointestinal). A major indication for immunomodulation of these drugs is combination with glucocorticoids for treatment of autoimmune diseases. Vinblastine is another vinca alkaloid that has been used to treat type II hypersensitivities, specifically immune-mediated hemolytic anemia (IMHA) and indomethacin. Like danazol, vinblastine appears to decrease expression of Fc (IgG) receptors on macrophages (Choudhry et al., 1995; Schreiber et al., 1987). The effects of vinblastine (weekly during induction followed by monthly during maintenance) when combined with danazol (given at 2 to 3 up to 10 mg/kg daily) proved effective for treatment of 63% of human patients with chronic idiopathic thrombocytopenic purpura (Choudhry et al., 1995).

Gold Therapy

Gold has been used for centuries as an elemental agent for the control of pruritis (Insel, 1995). Gold compounds are characterized by gold attached to sulfur (aurothio group) and include the more water-soluble compounds aurothioglucose and gold sodium thiomalate and the lipid-soluble compound auranofin. These compounds suppress or prevent inflammation of the joint and synovium associated with a number of infectious or chemical causes. The mechanism of action is not clear but may be inhibition of the maturation and function of mononuclear phagocytes and T cells. Gold is sequestered in mononuclear phagocytic cells. Other proposed but not generally accepted mechanisms include inhibition of prostaglandin synthesis, collagen linkage, complement activation, and a variety of lysosomal and other enzymes (Insel, 1995).

The disposition of the gold compounds has not been studied in animals other than humans; these data provide the basis of discussion. Disposition varies with water solubility. Water soluble-compounds (not prepared in oil) are rapidly absorbed after intramuscular administration, with peak concentrations occurring in 2 to 6 hours. Oral absorption is erratic and not predictable for the water-soluble compounds but is more predictable for auranofin, the hydrophobic compound. Distribution varies with the compound and duration of therapy. The gold is bound (95%) to albumin in blood, but eventually concentrations in selected tissues (inflammed synovium) approximate 10 times that in plasma. For the water-soluble gold compounds, elimination rate constants and half-lives also vary with dose. In humans, the plasma half-life is 7 days at 50-mg total dose, but it increases to several weeks to months with prolonged therapy. Concentrations can be detected in the blood for 60 to 80 days after therapy is discontinued and for up to 1 year in the urine. Concentrations probably are detectable in the liver and skin several to many years after therapy is discontinued. Excretion is predominantly (60 to 90%) renal, with the remaining eliminated in the feces. For auranofin, plasma concentrations tend to be lower and accumulation is much less (20%) than that of the water-soluble compounds, probably because of less tissue binding. Auranofin is eliminated principally in the feces.

Toxicity, manifested as skin or mucocutaneous lesions, occurs in 15% of human patients. Lesions include stomatitis, pharyngitis, tracheitis, colitis, gastritis, and vaginitis. Gray to blue pigmentation may occur in the skin. The likelihood of toxicity is concentration dependent but not based on gold concentration. Whereas proteinuria occurs in up to 50% of human patients receiving gold therapy, renal dysfunction (due to proximal tubular damage or gold-induced glomerulonephritis) occurs in 10% or less. Lesions tend to be resolvable if therapy is discontinued before damage is too severe. Thrombocytopenia, thought to reflect increased destruction, occurs in a very small percentage of human patients. A number of miscellaneous side or toxic effects that resolve when therapy has been discontinued also have been reported. These include encephalitis, peripheral neuritis, hepatitis, and pulmonary infiltrates. In general, although auranofin is better tolerated than the water-soluble compounds, the incidence of gastrointestinal disturbances (diarrhea, abdominal cramping) is greater. The incidence of side effects and their seriousness can be minimized by regular physical examination. In addition, therapy should be initiated with a small dose that is gradually increased to the maintenance dose. As the dose is increased, treatment should temporarily cease until clinical signs of moderate to severe toxicity resolve. The risk of restarting therapy should be balanced with the need for therapy. Antihistamines or glucocorticoids might decrease the incidence. Dimercaprol, a heavy metal chelating compound, can be used if severe side effects persist after therapy has been discontinued.

The major indication for chrysotherapy in human patients is rheumatoid or other arthritis that has not responded to NSAIDs or other therapy. The compounds slow the progression but do not cure disease. The usual human dose is 10 mg of the water-soluble compounds the first week followed by 25 mg the third and fourth weeks and 25 to 50 mg weekly thereafter to a cumulative 1-g dose. Response may take several months. The standard human dose for auranofin is 3 to 6 mg up to 9 mg administered divided two to three times or given once daily. Small animal doses are discussed with dermatologic disorders in this chapter.

Immunostimulant Drugs

Immunostimulants are indicated for immunodeficient animals. As with immune suppressants, stimulants can target either humoral or cell-mediated immunity. The lack of specificity has limited widespread use. In general, response to immunostimulants is mild.

Immunostimulants of Microbial Origin

Bacteria and fungal microbes generally nonspecifically stimulate several aspects of the immune response. Macrophage, cytotoxic T cell, T-cell (helper), and B-cell activities are enhanced, whereas T-cell suppressor cell activity is decreased. Enhanced activity reflects, in part, increased activity of chemical mediators such as tumor necrosis factor and interferon. The nonspecific enhancement of immune function can be used therapeutically. Adverse effects can be minimized by administration of killed organisms or selected microbial fractions, which stimulate the response while avoiding infection. A variety of mycobacterial products have been used to nonspecifically stimulate the immune system (Ford, 1986; Werner and Zerial, 1984). The classic biologic response modifiers include bacillus Calmette-Guérin and *Propionibacterium acnes (Corynebacterium parvum).*

Bacillus Calmette-Guérin

Bacillus Calmette-Guérin (BCG) is a live, attenuated strain of *Mycobacterium bovis* (Diasio and LoBuglio, 1995). Components of the bacterial cell wall of this organism activate B and primarily T cells; macrophage and neutrophil recruitment in response to lymphokine release results in a granulomatous reaction. The antiviral state induced by BCG appears to be essentially a nonspecific expression of a more or less prolonged stimulation of the immune system. The most likely mechanism for BCG's antiviral activity is direct stimulation of the mononuclear phagocytic system; however, specifically sensitized T lymphocytes that further activate macrophages are generated after a period of time. Stimulated macrophages release colony-stimulating factor, which contributes to macrophage regulation and IL-1, which promotes lymphocyte proliferation. The antiviral state is thus an indirect benefit of an essentially pathologic, although temporary, situation; the host is characterized by an increased ability to handle viral infections. Bacillus Calmette-Guérin requires at least 10 days after inoculation to enhance resistance against viral infections. The state of enhanced resistance is, however, long-lasting; repeated administrations (of nonliving product) may lead to a more prolonged and marked effect (Werner and Zerial, 1984).

Bacillus Calmette-Guérin has been used as an adjuvant in combination with tumor vaccines for dogs and cats. Tumors that undergo remission after BCG therapy may do so due to the release of tumor-specific antigens during nonspecific tumor lysis. The use of BCG has been studied in combination with a tumor vaccine. In human patients, use of BCG as an adjuvant for anticancer therapy has focused primarily on intravesicular administration in bladder cancer (Diasio and LoBuglio, 1995).

Muramyl Dipeptide

Muramyl dipeptide is a peptidoglycan and represents the smallest immunologically active component of the *Mycobacterium* cell wall. Like BCG, it nonspecifically enhances B-cell, T-cell, and macrophage activities. Because it is rapidly eliminated from the body, it is biologically modified to prolong its actions by incorporation into liposomes or conjugation with glycoproteins. Synthetic production has increased accessibility for clinical use. Use of this product when prepared as a liposomal product is discussed in Chapter 20.

*Regressin-V**

An emulsion of mycobacterial cell wall fractions, Regressin-V is licensed for the treatment of mixed mammary tumors and mammary adenocarcinoma in dogs and sarcoid in horses. The following information was supplied by the manufacturer. Regressin-V contains trehalose dimycolate and muramyl dipetide, which induce IL-1 and tumor necrosis factor-α secretion from monocytes and macrophages and activate T lymphocytes in a variety of species. In a study of seven dogs with mammary adenocarcinoma, complete remission was induced in five, with tumor-free survival times of 3 to 19 months; dogs were then lost to follow-up. There are no data suggesting that Regressin-V had any effect on metastatic disease.

The manufacturer recommends treating canine mammary tumors once 2 to 4 weeks before surgical excision. Fever and malaise may occur after injection. Surgical removal of the tumor creates cosmetic improvement (necrosis and draining of the tumor may be present for weeks); however, survival time is not significantly improved with surgery. If surgery is not performed, therapy can be repeated every 1 to 3 weeks for up to four treatments.

Propionibacterium Acnes

A killed suspension containing *Propionibacterium acnes* (formerly *Corynebacterium parvum:* Immunoregulin) has been approved for veterinary use (15 μg/kg IV biweekly for two to three treatments). Like BCG, it causes complex, nonspecific immunostimulation. Macrophage and cytotoxic T-cell activities are enhanced, as is antibody production by both thymus-dependent and thymus-independent antigens. Cell-mediated immunity is also stimulated. It is indicated for the treatment of clinical signs associated with virus-induced and bacteria-induced immunosuppression, such as that caused by feline leukemia virus (FeLV). The efficacy of *P. acnes* in the treatment of feline infectious peritonitis virus is questionable. One study has shown no difference in survival rate or mean survival time between untreated and treated animals experimentally infected with a high dose of feline infectious peritonitis virus. Studies investigating the antitumor effects of *Propionibacterium parvum* in dogs do not support its efficacy against early neoplasia, although it may be more effective in advanced disease when used in combination with other drugs (MacEwen, 1985). Cats infected with FeLV and afflicted with various non-neoplastic diseases showed some signs of response to treatment with *P. parvum* (Immunoregulin), although no cat reverted to an FeLV-negative status (Ford, 1986). Studies regarding the efficacy of *P. parvum* in FeLV-induced tumors apparently have not been done (MacEwen, 1985).

Staphylococcal Protein A

Staphylococcal protein A (SpA) is a cell wall polypeptide of *Staphylococcus aureus* Cowan I (SAC) that binds rapidly and with great affinity to immune complexes. Other regions of the molecule initiate T-lymphocyte and B-lymphocyte proliferation as well as secretion of soluble lymphocytic products such as interferon. Circulating immune complexes have been incriminated as "blocking factors" that aid in a tumor's escape from immunologic control. Therapeutic trials of the efficacy of SpA have been based on the hypothesis that removal of specific or nonspecific immunosuppressive molecules such as blocking factors will enhance host immune response to the tumor. Other regions of the SpA molecule initiate T-lymphocyte and B-lymphocyte proliferation and secretion of soluble lymphocyte products such as interferon. Treatment with SpA is achieved by extracorporeal perfusion of host plasma over whole SAC organisms or through filters containing purified SpA. Studies have shown that SpA or SAC treatment reduces tumor size, decreases levels of circulating immune complexes, and induces the appearance of cytotoxic antibodies directed toward neoplastic cells. A study utilizing SpA to treat FeLV-infected cats found that 50% of cats with FeLV-associated disease improved, and 33% of cats afflicted with malignant disease responded with reductions in tumor size as well as in bone marrow and peripheral blood neoplastic cells (MacEwen, 1985; Ford, 1986; Engelman et al., 1985, 1987). Viremia was cleared in 28% of treated cats. Circulation of a gamma-like interferon was demonstrated in some cats that responded to SpA and was followed by the appearance and rising titer of complement-dependent cytotoxic antibody. The antibody reacted with FeLV-infected cells and was specific for the major viral envelope glycoprotein gp70. The ability of cats to persistently remain FeLV negative appeared to correlate with the magnitude of FeLV antibody titer (MacEwen, 1985).

Mixed Bacterial Vaccines

Mixed bacterial vaccines composed of *Streptococcus pyogenes* and *Serratia marcescens* have been studied in cats with malignant mammary tumors. Although not statistically significant, survival time was greater (875 days) when surgery was combined with mixed bacterial vaccines versus surgery alone (450 days).

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*Prepared for inclusion in this chapter by S. Kruth (see Chapter 20).

Immunostimulants of Natural Origin

Cytokines

A number of cytokines produced by leukocytes and related cells actively regulate the immune system. Recombinant DNA technology (see Chapters 21 and 22) has led to widespread production and greater application of their use in the treatment of immunologically based disease. The cytokines most likely to be used for immunostimulatory effects include the interferons and selected interleukins.

Passive Immunotherapy: Antibodies

Passive immunotherapy with monoclonal or polyclonal antibodies has been investigated for both the diagnosis and therapy of cancers. Antibodies are directed toward surface antigens expressed by tumor cells. Specificity of antibodies (as long as immunoglobulins are derived from the species intended to be treated) should limit host toxicity to those cells expressing the antigen (i.e., tumor cells), thus avoiding systemic toxic effects. The antibodies themselves may be directly toxic to the cell or induce complement-dependent cytotoxicity. In addition, antibodies can be conjugated to drugs, toxins, or radioisotopes toxic to tumor cells, thus limiting the specificity of a variety of pharmaceuticals for tumor cells.

Immunoglobulins available in plasma obtained from donors generally contain detectable antibodies against bacterial, fungal, and viral pathogens (Diasio and LoBuglio, 1995). Passive transfer of resistance to the immunodeficient patient can be accomplished with intramuscular or intravenous administration. In human patients, the half-life of transferred immunoglobulins is approximately 3 weeks (Diasio and LoBuglio, 1995). Indications for human patients have included congenital or acquired states of immunodeficiency, selected hematologic disorders such as autoimmune hemolytic anemia, infectious viral diseases, and selected neoplastic diseases including chronic lymphocytic leukemia and multiple myeloma. Potential adverse reactions include anaphylaxis and transfer of infectious organisms (Diasio and LoBuglio, 1995).

Studies investigating the efficacy of passive immunotherapy on feline lymphosarcoma have thus far been limited to the use of polyclonal FeLV-neutralizing antibodies, feline oncornavirus-associated cell membrane antigen (FOCMA) antibodies, or both in cats afflicted with lymphosarcoma and leukemia. In one study, five of seven cats treated with both antibodies and six of eight cats treated with FOCMA antibodies alone underwent partial or complete regression of their disease (MacEwen, 1985). Additional studies by Cotter and coworkers (1980) suggest that polyclonal anti-FOCMA therapy combined with previously established chemotherapeutic regimens may improve remission time.

Monoclonal antibodies have been used to treat canine lymphosarcoma (see Chapter 18).

Human intravenous immunoglobulin (hIVIG) has been studied in dogs using in vitro (lymphocytes and monocytes) and in vivo (spontaneous immune-mediated diseases) methods. Prepared from plasma of healthy donors, it contains polyspecific IgG and is intended to treat primary immunodeficiencies. In vitro studies (Reagan et al., 1998) have shown hIVIG to bind to canine lymphocytes and monocytes and to inhibit through F_c-mediated binding monocyte phagocytosis, including that of antibody coated red blood cells. It is administered as an IV infusion (0.5 to 1.5 g/kg) over 6 to 12 hours, and animals must be closely monitored for signs of anaphylaxis or other adverse reactions (e.g., thromboembolism). Clinical evidence of efficacy exists for treatment of immune-mediated hemolytic anemia (Scott-Moncreif et al., 1997a, b), with treated dogs developing an increased hemoglobin and hematocrit up to 4 weeks after therapy. However, 50% of treated animals developed thrombocytopenia and 5 of 7 dogs that died had evidence of thromboembolism. Only 3 of 10 dogs were alive at 12 months, suggesting that long-term survival was not improved.

Miscellaneous Blood Components

Selective destruction of malignant lymphocytes occurs in several species in response to infusion of blood or blood components.

Antileukemic Activity Antileukemic activity (ALA) of humoral factors in serum, heparinized plasma, and whole blood has been documented in several species (MacEwen, 1985). Evidence suggests that ALA of blood constituents may be present in high concentrations in cryoprecipitates prepared from heparinized plasma. Physicochemical constituents of the cryoprecipitate that might be the source of ALA include cold-insoluble globulin, fibronectin, cell surface protein, large external transformation sensitive protein, and opsonic factor (MacEwen, 1985). A study in 32 cats revealed that of 24 treated with either normal cat serum or whole blood (20 mL/kg), 14 had a complete antileukemic response and 8 had a partial response. Of 10 treated with cryoprecipitate, 2 completely responded, and 6 had a partial response (Hayes et al., 1980).

Fibronectin Fibronectin injections have resulted in the regression of leukemic nodes in mice, suggesting that fibronectin may be the source of ALA. Fibronectin, a glycoprotein dimer, is a major protein of both blood and tissues; its most important function appears to be tissue remodeling during embryogenesis and wound healing. Antitumor activity may result from immunomodulation and modification of metastasis. Enhancement of opsonization increases the phagocytic ability of macrophages and monocytes, thus enhancing their tumoricidal activity. MacEwen (1985) studied the efficacy of fibronectin (0.5 to 2.0 mg/kg, IV, once daily) in 18 cats afflicted with lymphosarcoma. A 50% response rate was reported; one FeLV-positive cat converted to a negative status after treatment (MacEwen, 1985). A single case of mycosis fungoides in a cat responded to a combination of IV and intralesional fibronectin. Intralesional injections caused local epithelial necrosis, which reduced the tumor load by 75% and may have prevented systemic involvement (Caciolo et al., 1983).

Tumor Cell Vaccines

Tumor cells are thought to stimulate an immune response. This view is supported by the recognition that some tumors spontaneously regress; tumors are infiltrated with cells of the immune system, and the risk of cancer increases in the patient that is immunosuppressed. The antigenic potential of tumor cells is also the basis for the use of tumor cell vaccines. Tumor cell vaccines are most effective in the presence of residual disease and when combined with nonspecific immunomodulators. Jeglum and coworkers have treated cats afflicted with mammary adenocarcinoma using a combination of an autogenous tumor vaccine and BCG (see MacEwen, 1985). Although not significantly different, the mean survival time for each treatment group was least for those treated with surgery, BCG, and tumor cell vaccine compared with animals treated with either surgery alone or surgery with BCG. Additional studies with tumor cell vaccines are necessary before their efficacy can be established.

Hormonal Agents

Hormonal agents may offer a unique avenue of immunomodulation in viral diseases (Ford, 1986; Rosenthal, 1982). Hormones investigated for their immunomodulatory effects include prostaglandins and thymic proteins. Prostaglandins are local hormones that modulate both T and B lymphocytes. Prostaglandins, however, particularly PGE_2, are also immunosuppressants, and their role in immunopotentiation is limited. Thymosins are a group of endogenous substrates released from the thymus that stimulate the release of several pituitary neuropeptides. Thymic hormones induce maturation of T-cell precursors, promote differentiation and proliferation of mature T cells, and thus restore rather than potentiate the immune system. Several synthetic thymic peptides have been synthesized by either chemical means or genetic engineering techniques. The primary clinical application of these proteins is restoration of the immune system in the immunoincompetent (including virally induced) patient.

*Acemannan**

Acemannan (Acemannan Immunostimulant) is a long-chain polydispersed $\beta_{1,4}$-linked mannan-based polysaccharide derived from the *Aloe vera (barbadensis Miller)* plant. It stimulates the release of IL-1, IL-6, TNF-α, IFN-γ, and nitric oxide from macrophages, leading to tumor apoptosis and necrosis (Marshall et al., 1993; Ramamoorthy et al., 1996). Other actions include enhancement of macrophage phagocytosis and cytotoxicity and interference with glucosidase I activity (leading to the production of abnormal glycoproteins by neoplastic cells, which appears to be associated with tumor cell death). Direct antiviral activity is associated with modified glycosylation of both virus-infected cells and glycoprotein coats of viruses, leading to inhibition of virus infectivity and replication.

Acemannan is licensed for the treatment of fibrosarcoma in dogs and cats. Intratumoral injection induces tumor encapsulation and necrosis, facilitating surgical excision. The recommended dosage is 2 mg intratumorally and 1 mg/kg intraperitoneally weekly for 6 weeks. No adverse effects of acemannan have been reported at the recommended dosage. In one report, eight dogs and five cats with fibrosarcomas were treated with acemannan, surgical excision, and radiation therapy. Seven animals remained tumor-free at 440 to 603 days, with a median survival time of 372 days (King et al., 1995). In an earlier clinical report, a variety of other carcinomas and sarcomas were also reported to respond (Harris et al., 1991). It is not known what effect acemannan has on feline vaccine-associated sarcomas.

Acemannan has been used to treat cats with FeLV and feline immunovirus infections. Clinically affected cats treated with acemannan had improved quality of life and longer survival times than historical controls. Interestingly, oral administration of acemannan appeared to have the same efficacy as did parenteral administration similar to cats treated with low-dose oral recombinant human IFN-α.

Synthetic Immunostimulants

Levamisole

Levamisole, a phenylimidazothiazide anthelmintic, has been the subject of intense and controversial research as a biologic response modifier (Ford, 1986; Werner and Zerial, 1984). It is difficult to summarize the experimental and clinical data regarding the immunomodulating capabilities of levamisole. Levamisole has been regarded by some as a chemical agent capable of mimicking hormonal regulation of the immune system. It appears to stimulate recruitment and functions of macrophages and T cells, but only within a narrow range of doses and duration of administration in either the normal or immunoincompetent patient. Levamisole appears to alter cyclic nucleotide phosphodiesterases, decreasing cyclic guanosine monophosphate (cGMP) degradation and increasing cyclic adenosine monophosphate degradation. Elevated cGMP in lymphocytes enhances proliferation and secretory responses. Chemotaxis, phagocytosis, lymphokine synthesis, and the ratio of helper to suppressor T cells are increased. Levamisole does not appear to have any effect in immunocompetent animals. The modulatory effects of levamisole range from enhancement to inhibition with much strain, sex, age, and antigen variability. T-cell stimulation may be mediated by a soluble serum factor. Experimental studies generally have not supported the benefits of levamisole as have clinical studies. Levamisole 2 to 15 mg/kg was frequently tested prophylactically in experimental trials, however, as opposed to therapeutically (i.e., in infected patients) in clinical trials, suggesting that potential benefits of levamisole result from restoration of immunocompetence after virally induced immunosuppression. Indications for levamisole in human medicine include Hodgkin's disease and rheumatoid arthritis, and as an adjuvant chemotherapy of colorectal cancer (Diasio and LoBuglio, 1995). The use of levamisole for treatment of cancer in animals is not supported. In two studies involving more than 130 cats with malignant mammary tumors, levamisole (5 mg/kg orally on 3 alternate days per week) did not increase survival time or decrease recurrence rate (MacEwen et al., 1984). Levamisole causes adverse reactions typical of excessive cholinergic stimulation.

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*Prepared for inclusion in this chapter by S. Kruth (see Chapter 20).

Cimetidine

Histamine exerts immunomodulatory effects, including suppression of cytotoxic T lymphocytes, downregulation of cytokines, and activation of suppressor T lymphocytes (Hahm et al., 1996). Cimetidine is a histamine (H_2) receptor antagonist that experimentally enhances a variety of immunologic functions. Suppressor T lymphocytes possess H_2 receptors, which, when blocked, result in potentiation of cell-mediated immunity. Although more studies are indicated, cimetidine may be useful in a variety of conditions associated with immunosuppression. Because it selectively inhibits suppressor function, however, cimetidine also may prove deleterious to patients with autoimmune disorders.

The anticancer effects of cimetidine have been studied in selected human cancers. The H_2 receptor blockers have been studied for their effects on gastric cancer cells. Cimetidine but not famotidine exhibits antiproliferative effects on gastric cancer cells. Raniditine showed some inhibitory effects (Hahm et al., 1996). Cimetidine also appears to inhibit the growth of colorectal carcinoma (Adams and Morris, 1997); lymphocyte infiltration increases in the cancers and is associated with an improved survival in patients receiving the drug.

Miscellaneous Immunostimulants

A variety of compounds are capable of inducing IFN; however, the immunmodulating effects of the inducers are variable. For example, double-stranded IFN-inducing polyribonucleotides (poly I:C) cause immunostimulation, whereas tilorone, a simple synthetic IFN inducer, enhances antibody production while depressing cell-mediated immune responses. Many other drugs are in the experimental phases of drug development. The following addresses some of those drugs that may or may not ultimately become approved.

ABPP (Bropirimine)

ABPP (2-amino-5-bromo-6-phenyl-4[^{3}H]-pyrimidinone), approved for use in humans, is a potent inducer of IFN in several species. Hamilton et al. (1982) characterized the kinetics of ABPP and induced IFN in several species. They found that serum levels of IFN after treatment correlated well with serum concentrations of ABPP in the cat. ABPP was lethal in three of eight cats, however, at doses required to achieve minimal detectable levels of IFN. The authors postulated that the toxicity resulted from conversion of ABPP to phenolic derivitives that the cat excretes inefficiently.

Isoniplex

Isoniplex is an antiviral drug (see Chapter 12) that may also be used as an immunopotentiator in viral diseases (Ford, 1986; Werner and Zerial, 1984). Isoniplex enhances immune responses, including promotion of mitogen-stimulated T-lymphocyte proliferation and augmentation of antibody production and delayed-type hypersensitivity. The suggested mechanism of immunopotentiation by isoniplex begins with penetration of lymphocytes and suppression of viral RNA synthesis. It appears to support lymphocyte function by promoting RNA synthesis and translational ability. Further investigations regarding the use of isoniplex in viral infection should be anticipated because its efficacy results from an ideal combination of antiviral activity and immunopotentiation.

Promodulin

Promodulin is an experimental immunomodulating agent that has been subjected to clinical therapeutic trials for the treatment of cats concurrently infected with FeLV and feline infectious peritonitis (Ford, 1986). Cats were treated with 50 mg/kg up to 200 mg maximum dose IV once daily for 5 consecutive days. Although promodulin induced rapid remission of clinical signs associated with feline infectious peritonitis, (e.g., anorexia, fever, and serosal effusions), it did not appear to be effective in the treatment of concurrent FeLV infections. Cats that responded did so within 2 weeks of the final injection; the duration of clinical remission appeared to vary between 1 and 3 months. Clinical signs after exacerbation of disease did not respond to a second treatment regimen. Promodulin also was not effective in treating FeLV-induced solid tumors.

TREATMENT OF SPECIFIC IMMUNE-MEDIATED DISEASES

See also discussion of each syndrome in the appropriate chapter.

Type I Hypersensitivities

Anaphylaxis and Anaphylactoid Reactions

Clinical signs of systemic anaphylaxis include nausea, vomiting, diarrhea, pale mucous membranes, coolness to peripheral extremities, tachycardia, and tachypnea. Localized "anaphylaxis" results in clinical signs referable to the site of localized mast cell degranulation. Examples include angioneurotic edema resulting in swelling of lips, eyelids, and conjuctiva and urticarial lesions (or hives). Treatment is oriented toward preventing further mast cell degranulation, blocking the interaction between histamine (or other mediator) and tissue receptors, and antagonizing the physiologic response to mediators. Drugs that antagonize physiologic response also tend to further decrease mast cell degranulation. The goals of therapy for systemic anaphylaxis include cardiovascular and ventilatory support. Epinephrine is indicated to antagonize bronchoconstriction and provide cardiovascular support. Glucocorticoids (prednisolone sodium succinate) facilitate adrenergic receptor responses and decrease further mast cell mediator release. Histamine 1 (H_1) receptor antagonists (e.g., diphenhydramine) are of benefit only in preventing interaction of histamine and its receptors, not in preventing further mast cell degranulation.

Therapy is much more effective if administered in anticipation of mast cell degranulation (Thompson, 1995).

Allergic Respiratory Diseases

Allergic rhinitis is caused by inhaled allergens. The syndrome is unusual in dogs and cats and is commonly associated with atopy. Treatment may include glucocorticoids or H_1-receptor antagonists or a combination of the two.

Allergic bronchitis and pneumonitis are more common in dogs than cats. Chronic antigen stimulation causes accumulation of thick, tenacious mucus in the airways. Eosinophilic infiltration and resulting bronchiolitis and alveolitis can markedly contribute to the release of inflammatory mediators. Therapy is facilitated by administration of drugs that facilitate liquifaction and removal of secretions. Additional therapy includes glucocorticoids and bronchodilators.

Bronchial asthma occurs in cats and is discussed in Chapter 31.

Atopy

Atopy (allergic inhalant dermatitis, atopic dermatitis, and so forth) is an inherited syndrome associated with IgE production against environmental antigens. Antigens complex with IgE associated with mast cells in the skin, causing mast cell degranulation and the histopathology characteristic of this syndrome. Critical to understanding atopy is the recognition that each dog has a "threshold" response at which pruritis develops. Ideally, atopy is managed by recognition and removal of the antigen or hyposensitization. Medical therapy is less desirable because of limited success. Atopy is discussed more in depth in Chapter 33.

Type II Hypersensitivities: Antigen-Antibody Dependent Cytotoxicity

Immune-Mediated Hemolytic Anemia

Immune-mediated hemolytic anemia (IMHA) occurs as a result of increased red blood cell destruction mediated by the presence of an antibody on the membrane surface. The antigen to which the antibody binds is either of the red blood cell membrane or an exogenous antigen (e.g., drug or microbe) that has adhered to the surface. Immunoglobulins associated with IMHA in dogs generally are IgG or, less commonly, both IgG and IgM. In cats, IgM tends to be more common, with IgG alone causing IMHA in approximately 25% of cases. Complement activation is more likely with IgM-mediated IMHA. Antibody adherence and complement activation that are insufficient to cause erythrocyte lysis will result in damage and subsequent erythrophagocytosis of the deformed red blood cell (e.g., spherocyte). Intravascular hemolysis occurs when complement activation is extensive, leading to erythrocyte lysis. Released hemoglobin binds to serum haptoglobin, preventing glomerular filtration. If haptoglobin becomes saturated, however, free hemoglobin can be filtered. Renal toxicity can accompany intravascular IMHA due to antigen-antibody deposition or reaction in the basement membrane; free hemoglobin may also contribute to nephrotoxicity. Direct red blood cell agglutination or intravascular hemolysis increases the risk of thromboembolic disease.

Medical treatment of IMHA focuses on reducing phagocytosis of damaged or antibody-coated erythrocytes by reducing or blocking receptors on phagocytic cells, reducing or preventing the formation of more antibodies, and supportive therapy of complications associated with IMHA. Any likely inciting (exogenous) antigen (e.g., drug, microbe) should be removed. Immunosuppressive therapy with glucocorticoids is the cornerstone of therapy. Dexamethasone (0.1 to 0.2 mg/kg IV) every 12 hours is administered initially, followed by oral prednisolone (1 mg/kg every 12 hours) as the animal responds. Anemia and reduced oxygen delivery to the gastrointestinal tract may predispose the patient to gastrointestinal induced ulceration; preventative measures (e.g., H_2-receptor antagonists) should be considered. Danazol (5 to 10 mg/kg orally every 12 hours) may block Fc receptors on phagocytic cells, reducing red blood cell destruction (Holloway et al., 1990). Glucocorticoids will reduce macrophage phagocytosis and indirectly formation of antibodies; danazol also may be useful for blocking Fc receptors on phagocytic cells. Further reduction of red blood cell destruction may require administration of cyclophosphamide. Cyclophosphamide will also, however, increase the risk of thrombocytopenia and neutropenia (Gorman, 1995). Cyclophosphamide can be given as a single IV bolus (100 to 250 mg/m^2) in patients suffering from intravascular lysis or direct autoagglutination (Ward, 1996). This regimen also is particularly useful for patients that require a blood transfusion. Oral administration (50 mg/m^2 every 48 hours) is indicated in dogs that do not respond to glucocorticoid or danazol therapy. Efficacy of cyclophosphamide may not be realized until antibodies decline due to normal catabolism (generally 1 to 2 weeks) (Gorman, 1995).

Human gammaglobulin (0.5 to 1.5 g/kg IV over 6 to 12 hours) may prove useful for dogs that fail to respond to therapy (Scott-Moncrieff et al., 1997a, b). Cost may, however, be prohibitive and use may be limited by development of thrombocytopenia or thrombosis (see previous discussion). Cyclosporine may be of benefit in controlling the sequelae of IMHA that reflect tissue (and thus T-cell mediated) damage (Gorman, 1995). Blood transfusions should be avoided in patients with IMHA. Dogs with IMHA are predisposed to destruction of transfused red blood cells. Blood substitutes (oxyhemoglobin) may offer a viable alternative to prolonging or avoiding the need for blood transfusion. Although splenectomy should be considered as a surgical adjunct to medical management, removal of the spleen may also result in removal of an important site of extramedullary hematopoiesis.

Immune-Mediated Thrombocytopenia

Immune-mediated thrombocytopenia is a syndrome that occurs more commonly in dogs than cats and in males than females. It can occur in concert with other immune-mediated disorders, including IMHA (Gorman, 1995). Thrombocyte numbers can decline due to destruction (i.e., antibody/complement-mediated phagocytosis) or, less commonly, decreased formation of mature thrombocytes due to antibody/complement-mediated destruction of megakaryocytes (Gorman, 1995). As with IMHA, antibody can be directed to an endogenous or exogenous antigen adhered to the platelet or megakaryocyte. The primary clinical signs—which include and reflect inappropriate bleeding—generally do not occur until thrombocyte numbers have dropped below 30,000/μL. Bleeding is more likely with a rapid as opposed to a gradual decline.

Medical treatment focuses on prevention of bleeding, decreased destruction of thrombocytes, and restoration of thrombocyte numbers. Any likely inciting (exogenous) antigen (e.g., drug, microbe) should be removed. Glucocorticoids (either dexamethasone or prednisolone) are the first choice of therapy (see earlier discussion of IMHA) and, in general, cause thrombocyte counts to normalize within 1 week. Danazol also can be administered to reduce phagocytosis (Holloway et al., 1990; Bloom et al., 1989). Vincristine (0.75 mg/m^2 IV) can be administered if platelet numbers fail to increase to sufficient numbers. Once platelet numbers increase, vincristine should be discontinued and glucocorticoids continued for several more weeks (Gorman, 1995). Vincristine may be given after incubation with platelet-rich plasma in cases refractory to glucocorticoids, danazol, and vincristine. Presumably incubation allows vincristine to bind to platelets. Subsequent phagocytosis destroys the phagocytic cell, causing an overall reduction in platelet destruction (Helfand et al., 1984). If successful, the treatment may need to be repeated as new macrophage are generated. Platelet-rich plasma also can be administered in an attempt to restore platelet numbers to non–life-threatening concentration (>50,000/μL). The likelihood of immune-mediated thrombocytopenia relapse also may be reduced after infusion of platelet-rich plasma (Gorman, 1995). The use of vinblastine might be considered in relapsing patients (see discussion of cytotoxic drugs) based on effectiveness in human patients. Splenectomy is a surgical alternative or adjunct therapy that should be considered in refractory cases. Because of the risk of relapse, patients should be monitored periodically. Surgical neutering, particularly in females, may be indicated once platelet numbers have normalized.

Immune-Mediated Neutropenia

As with other immune-mediated hematopoietic diseases, glucocorticoids are indicated for neutropenia. Treatment can continue as described for IMHA.

The use of recombinant bone marrow growth factors (see Chapters 20 and 21) to increase bone marrow production of deficient cells is probably not wise unless the factor is derived from the species to be treated. Even in those situations, studies should confirm a lack of immune-mediated reactions when used in patients affected with an immune-mediated disorder.

Dermatologic Disorders

A number of immune-mediated skin diseases reflect a type II hypersensitivity. Included are pemphigus (foliaceus, erythematosus, vulgaris, vegetans), bullous pemphigoid, and dermatomyositis.

Pemphigus Disorders and Bullous Pemphigoid

Pemphigus disorders reflect the reaction of autoantibodies directed toward antigens located in the intercellular spaces between epidermal cells. The definitive antigen is not known but apparently is located in or near the cytoplasmic membrane (Gorman, 1995). The various types may reflect variants, crossovers, or altered presentations of the different forms of the disease. In all variants, antibody deposition causes the loss of adhesion between epidermal cells, leading to acanthosis. Complement activation results in local mast cell degranulation and an infiltration of inflammatory cells. Clinical signs vary within and among the variants and include visculobullous eruptions, cutaneous ulcerations, exfoliative lesions, and verrucous proliferations of the skin (Gorman, 1995). Bullous pemphigoid results from the generation of antibodies toward the lamina lucida of the basement membrane zone. As with pemphigus, complement activation may worsen the inflammatory response. Clinical signs include vesiculobullous lesions at mucocutaneous junctions, in the oral cavity, on footpads, and on the skin of the trunk, groin, axillae, and abdomen (Gorman, 1995).

Glucocorticoids can be expected to be effective in 40% of canine cases (Gorman, 1995) of pemphigus. The initial dose should be high (2 to 3 mg/kg orally every 12 hours for 10 to 14 days); the dose can gradually be reduced over 4 weeks (targeting 1 mg/kg orally every 48 hours) if an adequate response has occurred. Failure to respond or inability to decrease the dose of glucocorticoids is an indication for the addition of a second immunosuppressive drug. Generally, azathioprine (2 mg/kg orally every 24 hours) has been the first choice to combine with prednisolone (1 mg/kg orally every 12 hours). Response within 10 to 14 days will allow alternating the drugs each day at the same dose. Continued remission will allow a gradual reduction in the doses of both drugs to 1 mg/kg orally every other day, alternating the drugs daily (Gorman, 1995). Cyclophosphamide (50 mg/m^2 orally every 24 hours) can be combined with prednisolone (1 mg/kg orally every 12 hours) for 4 consecutive days each week for 2 to 3 weeks. If remission occurs, doses are gradually reduced to 1 mg/kg orally alternating drugs daily. Chlorambucil (0.1 mg/kg orally every 48 hours) can be used in lieu of cyclophosphamide; leukopenia and thrombocytopenia are potential side effects of this drug.

The third alternative for immunosuppressive chemotherapy is use of aurothioglucose initially in combination with prednisolone (1 to 2 mg/kg orally every 12 to 48 hours). Chrysotherapy should be initiated only after administration of an intramuscular test dose (1 mg for animals less than 10 kg; 5 mg for animals 10 kg or larger) twice, 1 week apart. Toxicity will be manifested as dermatitis, stomatitis, nephrotic syndrome, blood dyscrasias, eosinophilia, thrombocytopenia, and manifestations of allergic reactions. Therapy can be continued at 1 mg/kg weekly intramuscularly until remission; however, continued therapy should be based on an acceptable complete blood count. At that time, the interval is decreased to alternate weeks and finally monthly. Prednisolone therapy might be gradually phased out.

Pemphigus foliaceus in cats can be treated with chlorambucil as the first choice (Rhodes, 1995). Daily therapy (0.1 to 0.2 mg/kg/day) should be continued until lesions have markedly reduced, which may take 4 to 8 weeks. Alternate-day therapy should be implemented when approximately 75% improvement occurs and continued for several weeks. Complete blood counts should be monitored every 2 weeks of chlorambucil therapy (Rhodes, 1995).

Dermatomyositis

Dermatomyositis might be classified as an inflammatory muscle syndrome. Unlike polymyositis, which appears to involve a cell-mediated, antigen-specific response, dermatomyositis appears to reflect an abnormality of the humoral response, resulting in vasculitis. In human patients, treatment with low-dose methotrexate has proved beneficial (Langford et al., 1998a, b). Dermatomyositis in veterinary medicine is an inherited idiopathic inflammatory syndrome affecting collies, Shetland sheepdogs, and their crosses. Skin lesions include erythma, scaling, and crusting, particularly around the eyes, tips of the ears and tail, digits, and carpal and tarsal regions. Pentoxifylline, a methylxanthine derivative, has been recommended (Rees and Boothe, 1999) based on potential efficacy in people (Asanuma et al., 1997). Studies of the drug in dogs suggest a higher dose than that for humans and a twice to three times daily dosing interval should be used. Clinically, response may take several weeks. The drug appears to be well tolerated by dogs. Clinical trials in collies with dermatomyositis are currently under way.

Feline Eosinophilic Granuloma Complex

Eosinophilic granulomas may respond to glucocorticoids. Direct lesional injection of methylprednisolone acetate (2 mg/kg, minimum of 20 mg) every 2 weeks is the preferred method of administration. High oral doses of prednisolone may be an effective alternative (Rosenkrantz, 1991). Response to chlorambucil has been reported (Rhodes, 1995) within 6 weeks of therapy (0.1 to 0.2 mg/kg per day). Response to therapy should be followed by a 12-week period during which the dose of chlorambucil is decreased until discontinued. Megestrol acetate is an undesirable alternative unless the patient has proved refractory to other modalities, including chlorambucil. Urine should be monitored for glucose in order to detect the development of diabetes mellitus. Levamisole (2.2 mg/kg orally every 48 hours) has been reported to cause some (but incomplete) remission in some cases (Rosenkrantz, 1991; Messinger, 1995). Additionally, accurate dosing is difficult because of the large tablet size (184 mg). Cats often react adversely, with transient anorexia, vomiting, and hypersalivation being the most common side effects. Bone marrow suppression can be marked and is characterized by a long recovery period.

Type III Hypersensitivities: Immune Complex Disease

Systemic Lupus Erythematosus

The deposition of circulating autoantibodies or autoantibody-antigen complexes in the endothelium, particularly that of the glomerulus, appears to initiate complement-mediated inflammation. The inflammatory site is infiltrated by immune cells. In the glomerulus, response includes proliferation of capillary cells, thickening of the basement membrane, and scarring. Other vascular beds affected include the skin, serous membranes, synovial tissues, and cutaneous and visceral blood vessels (Langford et al., 1998a, b). Soluble immune complexes are more problematic than large immune complexes, which precipitate and are rapidly phagocytized. Soluble complexes are able to penetrate deep into vascular endothelial channels, activate complement, and stimulate an inflammatory response. In humans, intravenous cyclophosphamide has been established as the treatment of choice for lupus-induced nephritis. Bolus cyclophosphamide has also, however, proved effective for lupus affecting other body systems, including the central nervous system, lungs, and arteries. Azathioprine and weekly methotrexate are effective for treating human lupus that does not involve major organs, such as rashes, serositis, and arthritis, or in combination with glucocorticoids to reduce the glucocorticoid dose. Cyclosporine apparently has not been studied for treatment of systemic lupus erythematosus, although clinical response has been reported (Langford et al., 1998a, b).

Because systemic lupus erythematosus can be polysystemic in its presentation, the sequelae of immune complex deposition associated with systemic lupus erythematosus can affect a number of body systems, resulting in the need for medical management of secondary disease. Examples include but are not limited to glomerulonephritis, arthritis, and vasculitis. The reader is referred to the chapters that address these specific body systems for information on management of the sequelae of inflammatory disease. Treatment for the immune-mediated aspect of the disease is the same as for pemphigus skin disorders.

Cutaneous Discoid Lupus Erythematosus

Considered a mild form of systemic lupus erythematosus, cutaneous discoid lupus erythematosus is not accompanied by systemic involvement. The most common form presents as a nasal dermatitis; skin surrounding the eyes, pinnae, lip, and feet may also be involved. Treatment includes immunosuppressive doses of glucocorticoids as described for other immune-mediated diseases, although a lower initial dose may be effective (1 mg/kg orally twice daily). Vitamin E (400 IU orally 2 hours before or after a meal every 12 hours; acetate or succinate) may be effective as the sole agent; however, a 30- to 60-day lag time to efficacy mandates that initial therapy include glucocorticoids. Topical glucocorticoids may be effective in mild cases. Minimizing exposure to the sun, including using topical sunscreen, or other ultraviolet light also will be helpful, particularly in animals with depigmentation. Niacin or tetracycline (5 to 12 mg/kg orally every 8 hours) was reportedly effective in 70% of cases in one study.

Rheumatoid Arthritis and Other Arthritides

The rheumatoid factor is an antibody that reacts with IgG that has bound to antigen and subsequently undergone a conformation change. The reason for selectivity in joints is not understood. In humans, drugs used to treat rheumatoid arthritis include gold compounds or penicillamine and cytotoxic drugs, including azathioprine, cyclophosphamide, and methotrexate. Since the late 1980s, low-dose weekly methotrexate has become the preferred medication (Langford et al., 1998). Methotrexate has proved more rapid in onset. Because it is safer than traditional cytotoxic drugs, treatment generally can progress for a longer period of time. Because functional disabilities and progress of the disease occur rapidly in the first years of disease in humans, cytotoxic drugs are begun early. Drug combinations have been advocated because of the possibility of synergistic effects. Examples include methotrexate with sulfasalazine, cyclosporine, or biologic agents. Treatment in animals has not been as well investigated and focuses on control of inflammation with glucocorticoids and, if necessary, aspirin. The use of glucocorticoids is supported by the rapid clinical improvement and decrease in IL-6 activity documented in dogs with juvenile polyarthritis syndrome (Hogenesch et al., 1995). The use of other immunosuppressive drugs in animals (azathioprine, cyclophosphamide) has been reserved for severe cases. Based on findings in humans, however, a more aggressive approach may be warranted. Disease-modifying agents (e.g., glucosamine and chondroitin sulfates) should be used to support cartilage repair.

Feline chronic progressive polyarthritis is associated with feline leukemia virus and feline syncytia–forming virus and most commonly presents as osteopenia and periosteal bone proliferation around affected joints. Less commonly, joints are characterized by subchondral marginal erosions, similar to those of rheumatoid arthritis. Rheumatoid factor cannot be identified, however. Treatment includes immunosuppressive doses of corticosteroids (1 to 3 mg/kg orally every 12 hours). Nonresponders may require treatment with chlorambucil, cyclophosphamide, or azathioprine. As previously suggested, disease-modifying agents may prove beneficial.

Type IV Hypersensitivities: The Delayed Response

Allergic Contact Dermatitis

Allergic contact dermatitis is the most common type IV hypersensitivity recognized in small animals, being responsible for up to 10% of dermatologic cases (Gorman, 1995). The syndrome is initiated when the skin comes in contact with the inciting antigen or chemical. Actual chemicals that cause contact dermatitis are not known, but it is likely that the chemical acts as a hapten that subsequently covalently bonds to a protein. The location of the protein is not clear but is probably associated with the class II molecule of an APC, which in the skin is the Langerhans' cell. Sensitization generally requires 4 to 10 days; subsequent exposure to the chemical results in a marked T-cell–mediated response (Gorman, 1995). Treatment is best implemented by removal of the inciting antigen and short-term (7-day) administration of prednisolone (0.5 to 1 mg/kg every 12 to 24 hours).

Inflammatory Myopathies

In humans, polymyositis appears to reflect cell-mediated, antigen-specific cytotoxicity, with azathioprine being the only cytotoxic drug to be of benefit in controlled studies. Low-dose methotrexate or azathioprine with high-dose glucocorticoid therapy has become the standard therapy. Combinations of methotrexate and either cyclophosphamide or cyclosporine may be effective and are being studied (Langford et al., 1998a, b).

Inflammatory Bowel Disease

The use of immune-modifying therapy for human patients with inflammatory bowel disease (IBD) became popular only in the 1990s (Sandborn, 1995, 1996; Langford et al., 1998a, b). Controlled clinical trials in humans have focused on azathioprine, 6-mercaptopurine, cyclosporine, and methotrexate. Azathioprine or 6-mercaptopurine has been effective for treatment of Crohn's disease, although efficacy depends on duration of therapy; at least 13 and more often 17 weeks of therapy is required before the drugs reach their full effects.

Intravenous administration of azothioprine may decrease the time to response. Cyclosporine has been studied at low doses (<1 mg/kg per day) or high doses (>5 mg/kg per day) to minimize the risk of nephrotoxicity (less of a concern in veterinary patients) but has proved of little benefit in Crohn's disease. It has been more effective for treatment of ulcerative colitis at high doses (8 to 10 mg/kg per day), although only a few patients have been studied. Cyclosporine concentrations in responding patients were above 250 ng/mL. Methotrexate appears to be useful for both induction of remission and steroid sparing in patients with both Crohn's disease and ulcerative colitis. Combinations of drugs also have been studied. Azathioprine and 6-mercaptopurine should not be used in combination with methotrexate because of the increased risk of toxicity. Cyclosporine and methotrexate have been used in human patients with IBD with some success.

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20

Biologic Response Modifiers: Interferons, Interleukins, Recombinant Products, and Liposomal Products[*]

Stephen A. Kruth

BIOLOGIC RESPONSE MODIFIERS AND CYTOKINES

INTERFERONS

Interferon Biology

Interferons as Therapeutic Agents

  Feline Infectious Peritonitis

  Feline Leukemia Virus and Feline Immunodeficiency Virus

  Low-Dose Oral Recombinant Human Interferon-α

  Interferons as Therapy for Cancer

INTERLEUKINS

Interleukin Biology

Examples of Interleukin Therapy in Dogs and Cats

  Interleukin-1

  Interleukin-2

  Other Interleukins

HEMATOPOIETIC GROWTH FACTORS

Recombinant Human Erythropoietin

Growth Factors Affecting Myeloid Lineages

Granulocyte Colony-Stimulating Factor

  Granulocyte/Macrophage Colony-Stimulating Factor

  Other Hematopoietic Growth Factors Not Yet Available for Clinical Use

LIPOSOMAL PRODUCTS

EXAMPLES OF BIOLOGIC RESPONSE MODIFIERS LICENSED FOR USE IN DOGS AND CATS

SUMMARY

BIOLOGIC RESPONSE MODIFIERS AND CYTOKINES

Natural or synthetic preparations given with the intent of altering the response of the host to a pathogen, neoplasm, or inflammatory process have been termed *biologic response modifiers.* The goal of therapy may be to increase the effectiveness of the immune response directed toward a pathogen or neoplasm, to stimulate the proliferation of hematopoietic progenitor cells (e.g., in the treatment of chemotherapy-associated neutropenia), or to decrease a chronic inflammatory response (e.g., chronic inflammatory bowel disease). Biologic response modifiers are not usually specific in an immunologic sense; rather, they alter physiologic systems through changes in regulatory pathways. They range from bacterial cell wall extracts to molecularly cloned cytokines. As mediators of physiologic processes, interferons and interleukins are candidates for therapeutic manipulation or even to be given as drugs. Several recombinant human cytokines are commercially available in pharmacologic quantities and are available for veterinary use (Table 20–1). Recombinant technology and its importance in veterinary medicine are addressed more in depth elsewhere (see Chapter 21). Many other human, bovine, porcine, ovine, and some canine and feline (Table 20–2) cytokines have been characterized and used in clinical research. Some generalizations about cytokine biology follow. See the reviews by Aggarwal and Puri (1995), Nicola (1994), and Hilton (1994) for general discussions of cytokine biology.

Cytokines are polypeptides that regulate cell growth and differentiation, apoptosis, inflammation, immunity, and repair. They are of fundamental importance in the pathogenesis and treatment of disease. They transmit information to target cells regarding the physiologic status of the animal, resulting in a biologic response in the target tissue. More than 50 distinct human cytokines and their receptors have been described. Cytokine nomenclature can be bewildering, with several historical names attached to the same molecule (e.g., *stem cell factor, c-kit ligand,* and *mast cell growth factor* are all the same cytokine). A World Health Organization nomenclature system helps to clarify cytokine naming, and Internet resources such as the Cytokine Explorer (hftp://kbot.mig.missouri.edu:443/cytokines/explorer.htmi) are useful for finding synonyms and other information about cytokines of veterinary interest.

Cytokines can be categorized into families based on homology in primary amino acid sequence, three-dimensional structure, induction mechanisms, chromosomal location, similarities in receptor type, and functional homology. Families that are currently clinically relevant in companion animal medicine include interferons (IFNs; having antiviral and immunoregulatory functions), interleukins (ILs; having a wide variety of functions), and hematopoietic growth factors.

Most cytokines are not constitutively produced but are secreted after activation of cells by viral, bacterial, and parasitic infections. The cellular sources of most cytokines are diverse, with production occurring in many types of cells. Production is normally short lived, usually for hours to a few days. Normally, they have autocrine and paracrine (rather than endocrine) effects, with little to no detectable circulating levels. Because of high cytokine-receptor affinity, cytokines are effective in the picogram to nanogram per mL range.

Cytokines typically have pleiotropic and redundant ac-

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[*] From Kruth SA: Biological response modifiers: interferons, interleukins, recombinant products, liposomal products. Vet Clin North Am Small Anim Pract 1998; 28: 269–295.

Table 20-1. Commercially Available Recombinant Human Cytokine Interferons

- Interferons
  - Alfa-2a (Roferon-A)
  - Alfa-2b (Intron A)
  - Alpha-n1 (nonrecombinant; Wellferon)
  - Alfa-n3 (nonrecombinant; Alferon N)
  - Beta-1b (Betaseron)
  - Gamma-1b (Actimmune)
- Interleukin-2 (Proleukin)
- Hematopoietic growth factors
  - Erythropoietin (epoetin alfa; Epogen, Procrit, Eprex)
  - G-CSF (filgrastim; Neupogen)
  - GM-CSF (sargramostim; Leukine, Prokine)

G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte/macrophage colony-stimulating factor.

tions. The same activity may be induced by several structurally distinct cytokines acting at unrelated cell surface receptors. For example, IL-1, tumor necrosis factor-α (TNF-α)* and IL-6 are all mediators of the acute inflammatory response; induce fever and the synthesis of acute-phase proteins in the liver; increase vascular permeability; and induce adhesion molecules, fibroblast proliferation, platelet production, IL-6 and IL-8, and T- and B-cell activation. Gene deletion experiments reveal that few individual cytokines are absolutely essential to life or even to individual cell function. Also, the cellular response of most cytokines is modulated by other cytokines, with synergistic, additive, and antagonistic interactions described. Cytokines form a complex feedback network by either inducing or suppressing the expression of other cytokines, forming cascades similar to the blood coagulation cascades.

Structurally, most cytokines consist of a single glycosylated polypeptide chain. They interact with cells by binding to specific high affinity cell surface receptors. The intracellular signal transduction cascade initiated by binding of a cytokine to its receptor eventually results in the production of DNA-binding proteins that influence transcription of various genes. In addition to cell surface receptors, soluble receptors have been described for many cytokines. Soluble receptors may be involved in cytokine transport or inhibit cytokine activity.

Table 20-2. Cloned Canine and Feline Cytokine Genes or cDNA*

- Canine cytokines
  - Interferon-γ (Devos et al., 1992; Zucker et al., 1992, 1993)
  - Interleukin-2 (Dunham et al., 1995; Knapp et al., 1995)
  - Interleukin-8 (Ishikawa et al., 1993; Matsumoto et al., 1994)
  - G-CSF (Zinki et al., 1992)
  - GM-CSF (Nash et al., 1994)
  - Stem cell factor (Shull et al., 1992)
  - Megakaryocyte growth and development factor (Bartley et al., 1994)
  - TNF-α (Zucker et al., 1994)
- Feline cytokines
  - Interferon-α (Nakamura et al., 1992; Sakurai et al., 1992; Ueda et al., 1993a,b)
  - Interferon-γ (Argyle et al., 1995; Schijns et al., 1995b)
  - Interleukin-2 (Cozzi et al., 1993)
  - Interleukin-4 (Schijns et al., 1995b)
  - Interleukin-6 (Bradley et al., 1993; Ohashi et al., 1993)
  - TNF-α (Rimstad et al., 1995)

*None are commercially available.

A number of proteins that inhibit the activity of cytokines have been reported. The best characterized is the IL-1 receptor antagonist (IL-1 Ra), which binds to receptor but fails to activate the cell. IL-1 Ra is currently being investigated as a therapy for rheumatoid arthritis in humans and may have a role in the treatment of other inflammatory disorders if appropriate delivery systems can be developed. A second way in which a cytokine can be inhibited is by binding of soluble cytokine receptors that are able to bind the cytokine and neutralize its activity, as discussed earlier.

Recombinant DNA technology has been used to produce cytokines, some of which are commercially available. The recombinant process involves cloning the cDNA encoding the protein of interest and placing it into an expression system (bacterial, yeast, insect, mammalian cell culture) under conditions such that large amounts of the protein are produced. By convention, these products are designated by an "r" preceding the name of the cytokine and a designation of the species of origin (e.g., rhIL indicates recombinant interleukin of human origin, and rfe-IFN indicates a recombinant interferon of feline origin). Most cytokines are conserved in the evolutionary sense, and biologic effects occur when human recombinant products are administered to companion animals.

It is tempting to administer cytokines in pharmacologic doses; however, several points need to be considered. Perhaps most importantly, systemic levels of a given cytokine will perturb many cytokine cascades, with resultant side effects and toxicity. Dosing may be critical; for example, low doses of IFN appear to be immunostimulating, whereas higher doses are immunosuppressive, and the specific type of IFN influences these effects. Currently, recommended cytokine doses are empirically derived. With the exceptions of rfeIFN-α (in cats) and rhIL-1 (in dogs), the pharmacokinetics of cytokines in dogs and cats have not been investigated.

The safety and efficacy of cytokines as biologic response modifiers may be improved if they can be delivered directly to target cells. Delivery systems, such as liposomes, have been reported in the veterinary literature, with encouraging results. In some cases, the cDNA for the cytokine of interest can be delivered (using a variety of methods) directly to the tissue of concern (usually a neoplasm), and controlled expression of the gene may confer clinical benefits. Both agonistic and antagonistic peptides have been sought for various cytokines in attempts to achieve systemic oral administration or to suppress harmful effects. Biologically active peptide analogues of human IL-1, IL-6, TNF-α, and IFN-γ have been reported.

INTERFERONS

Interferon Biology

Interferons are cytokines secreted by virus-infected cells and were originally characterized by their nonspecific antiviral activity. Interferons bind to receptors on other cells and induce antiviral proteins, protecting those cells from infection. It is now known that IFNs induce a wide range of pleiotropic effects, including antiviral, antitumor, antiparasitic, and immunomodulatory effects.

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*Tumor necrosis factor (TNF)-α is a multifunctional cytokine with biologic activities that include modulation of tumor growth, infections, septic shock/systemic inflammatory response syndrome, and autoimmunity. The TNF family of cytokines is distinct from the interleukin and interferon families. Canine and feline TNF-α have been cloned. They are not discussed in this chapter.

Two distinct classes of IFNs have been described. Class I interferons are subdivided into alpha, omega, and beta interferons (a subclass of omega interferons, the tau interferons, has been described in ruminant embryos and is important in maintaining pregnancy). Class II interferons are composed of a single protein, IFN-γ. IFN-α and IFN-ω were originally described as being secreted by leukocytes, but they are likely produced by all nucleated cells. Humans have at least 24 different alpha and omega genes, dogs have two alpha genes and no omega genes, and the genetic complement of cats has not been reported. Feline IFN-α cDNA has been cloned and the cytokine produced in a silkworm-recombinant baculovirus system, and its pharmacokinetic properties have been studied (Nakamura et al., 1992; Sakurai et al., 1992; Ueda et al., 1993a,b). The pharmacokinetic data suggest that rfeIFN has similar pharmacokinetic properties to human interferons and that it is distributed primarily to the liver and kidneys, is rapidly catabolized mainly in the kidneys, and is excreted in the urine without residual accumulation in the body. Interferon-β is classically described as being produced by fibroblasts; however, many other cells can be stimulated to secrete the cytokine. Humans and dogs have one IFN-β gene. Synthesis of IFN-α and IFN-β can be induced by live or inactivated viruses, bacterial cell walls, synthetic oligonucleotides, IL-1, IL-2, and TNF-α. IFN-α and IFN-β compete for similar receptors. IFN-γ is produced by activated T and natural killer (NK) cells and is structurally and functionally distinct from IFN-α/β. All mammals investigated have only one IFN-γ gene. IFN-γ binds to a receptor distinct from the α/β receptor. Canine IFN-γ has been characterized, the cDNA and chromosomal gene have been cloned, and production and characterization of recombinant canine from *Escherichia coli* has been described (Devos et al., 1992; Fuller et al., 1992; Zucker et al., 1993; Atkins and Mier, 1993; Cozzi et al., 1995). Feline IFN-γ cDNA has also been cloned (Argyle et al., 1995; Schijns et al., 1995a).

After receptor binding, interferons induce the transcription of a set of genes called *IFN-stimulated genes* (ISGs). Nearly 30 different ISGs have been identified. Induction of ISGs by IFN-α/β is rapid and transient, lasting for 3 to 4 hours. IFN-γ requires several hours of exposure before gene induction occurs. After the initial induction, ISG transcription declines and returns to basal levels.

Interferons inhibit the growth of almost all known viruses by interfering with viral RNA and protein synthesis. Interferons are induced by viral nucleic acid and bind to the receptors of nearby cells. The development of resistance to virus infections occurs within a few minutes and peaks within a few hours. Several proteins are induced, including RNase L (which cleaves viral RNA), nitric oxide synthetase (nitric oxide has antiviral activity), a protein kinase that phosphorylates an initiation factor called eIL-2 (which inhibits viral protein synthesis by preventing the elongation of viral double-stranded RNA), and the Mx protein, which inhibits translation of viral mRNA (Tizard, 1996). IFN-γ inhibits viral replication by stimulating the release of other IFNs. Interferons are also induced by bacteria, fungi, and some protozoa, and the activation of phagocytic cells is important in the host response to these pathogens.

Interferons induce increased expression of class I and class II MHC molecules on antigen-presenting cells, leading to enhanced antigen presentation. They increase phagocytosis and intracellular and extracellular killing by macrophages and neutrophils. The interferons also modulate T, B, and NK cell function, with IFN-γ having the most potent immunomodulating activity.

Interferons have several effects on neoplastic cells, including modulation of oncogene expression. Down-regulation of c-myc, c-fos, c-Ha-ras, c-mos, and c-src have been described in various models. IFN-α augments NK cell cytotoxicity against neoplastic cells and acts synergistically with IL-2 to increase NK activity. Antiangiogenic activity has also been described.

Large-scale production of IFNs is accomplished by culturing stimulated cells, leading to the production of "natural" or "native" interferon (denoted by "N") products. Alternatively, IFNs can be produced by recombinant methods. Human interferons from both sources are commercially available. Natural IFNs are less concentrated and may contain a mixture of interferon types with other cytokines. An excellent comprehensive review of interferon biology of species of veterinary interest has been published by Tizard (1995).

Interferons as Therapeutic Agents

In humans, IFN-α has been approved for the treatment of hairy cell leukemia, chronic myelogenous leukemia, Kaposi sarcoma, basal cell carcinoma, renal cell carcinoma, and genital warts. Effects on metastatic melanoma, endocrine-pancreatic tumors, metastatic colorectal and ovarian carcinoma, and bladder cancer have also been reported. Interferon-α is also licensed for the treatment of chronic hepatitis B. Interferon-β has been approved for the treatment of multiple sclerosis and IFN-γ for the treatment of chronic granulomatous disease.

Using a feline in vitro system, Weiss and Oostrom Ram (1990) showed that low levels of rhIFN-α had no effect on lymphocyte blastogenesis, whereas higher levels significantly suppressed blastogenic responses. In vivo, cats given 10^2 or 10^4 IU/kg had significantly enhanced blastogenesis, whereas cats given 1×10^6 IU/kg had depressed lymphocyte stimulation. In cats, the immunomodulating effects of rhIFN-α appeared to be dose dependent.

Activity of rfeIFN-α against rotavirus, feline panleukopenia virus, feline calicivirus, and feline infectious peritonitis coronavirus was documented in cell cultures of feline origin. The antiviral effect was more pronounced when the cell cultures were treated continuously than when they were pretreated only before challenge. rfeIFN did not have activity in canine cells challenged with vesicular stomatitis virus, implying species specificity of action (Mochizuki et al., 1994). This product is marketed in Japan as Intercat.

Feline Infectious Peritonitis

Parenterally administered rhIFN-α and IFN-β, with or without *Propionibacterium acnes* (which enhances IFN responses and augments T- and NK-cell activities) given prophylactically or therapeutically did not significantly reduce the mortality rate of experimentally induced feline infectious peritonitis virus (FIPV) infection. Cats treated with high-dose IFN, 10 U/kg daily for 8 days and then on alternate days for an additional 2 to 3 weeks, however, had temporary suppression of clinical signs and decreased serum antibody responses to FIPV, and the mean survival time of cats treated with high-dose rhIFN-α was increased by a few weeks over that of untreated cats. Interferon-related toxicities were not reported (Weiss et al., 1990). It is possible that the benefits of the high-dose protocol were due to the dose-dependent immunosuppressive effects of IFN. The increase in survival times in this study using experimental challenge were only 2 to 3 weeks, and there are few data documenting the response of cats with naturally occurring disease. There are anecdotal reports of orally administered low-dose rhIFN-α therapy (as described below) inducing remissions from clinical FIP; however, the true benefit of rhIFN-α in cats with spontaneously occurring FIP is unknown, and conventional therapy with cytotoxic drugs and corticosteroids is still the treatment of choice (Weiss, 1994, 1995).

Feline Leukemia Virus and Feline Immunodeficiency Virus

The parenteral administration of rhIFN-α in combination with zidovudine (AZT) beginning at the time of exposure to feline leukemia virus (FeLV) or feline immunodeficiency virus (FIV) abrogated the progression of viral infection and protected treated animals from induction of persistent antigenemia and disease. The anti-FeLV effect was limited by the production of anti–rhIFN-α antibodies detected 7 weeks after the start of therapy. Interferon-associated toxicity was not observed (Zeidner et al., 1990). In a subsequent study, AZT, IFN-α, and adoptive transfer of lectin/IL-2–activated lymphocytes were cleared of their viremia and remained clean even after anti-IFN antibodies developed. Combination therapy appeared to reconstitute antiviral humoral immunity, counteracted immunosuppression, and induced the reversal of retroviremia (Zeidner et al., 1993). Unfortunately, due to the problem of antibody induction, parenteral rhIFN-α appears to have little, if any, clinical utility as monotherapy for FeLV infections.

Low-Dose Oral Recombinant Human Interferon-α

In 1988, Cummins et al. reported that, following experimental infection with the Rickard strain of FeLV, the administration of 0.5 or 5 U of natural hIFN-α orally once daily for 7 consecutive days on alternate weeks for 1 month was associated with survival in 70% of IFN-treated cats, whereas 100% of placebo-treated control cats died. Twelve of 13 cats treated with IFN did develop persistent viremia. In another report, four cats with FeLV-associated nonregenerative anemia were treated with 100,000 U bovine IFN-β orally for 5 consecutive days on alternate weeks. General clinical improvement, reduction in circulating antigen levels, and normalization of hematocrit levels were reported in all cats (Tompkins and Cummins, 1982), and one cat cleared its viremia. Similar findings were reported by Steed (1987), who treated FeLV-infected cats with low-dose natural hIFN-α or bovine IFN-β. Weiss et al. (1991) reported 69 FeLV-infected cats with clinical signs treated orally with either low-dose rhIFN-α or bovine IFN-β. Cats treated with rhIFN had significantly higher survival rates than did cats given bovine interferon; both groups had increased survival compared with historical controls. In general, clinical responses were observed within the first or second week of oral IFN administration, with increased appetite, greater activity, weight gain, resolution of fever, improved hemogram and leukocyte counts, and quicker recovery from secondary bacterial infections when antibiotics were administered. Most cats remained viremic; however, some seroconverted. Other anecdotal data suggest that rhIFN-α confers clinical benefit to cats symptomatic for FeLV infections; however, there are no controlled studies with naturally occurring infections.

In contrast to the above reports, Kochiba et al. (1995) reported that low-dose oral hIFN-α had no significant effects on viremia, course of the disease, or differential leukocyte counts in experimental FeLV infection. In their system, the Kawakami-Theilen strain (A, B, and C subgroups, which consistently induce fatal erythroid aplasia) was administered to 12-week-old kittens. Methylprednisolone acetate was also given the day of inoculation. Neither rhIFN-α nor human natural IFN-α induced any significant benefit compared with placebo. Also, low-dose oral rhIFN-α administered to humans did not appear to have any significant immunomodulatory or antitumor activity (Kochiba et al., 1995). Efficacy of oral IFN-α in humans with human immunodeficiency virus infection has been suggested, but not confirmed (Kociba et al., 1995).

If orally administered low-dose human IFN-α has any effect in cats with retroviral infections, a direct systemic antiviral effect is unlikely. It may be possible that interferon may be acting as a biologic response modifier following binding to cellular receptors in the oral cavity/pharynx, triggering cytokine cascades that have systemic immunomodulatory effects. Appetite stimulation may be due to direct central nervous system effects. When used orally in cats, adverse effects have not been reported, and anti-rhIFN-α neutralizing antibodies do not appear to develop.

The dosage of IFN is 30 IU rhIFN-α *per cat* orally once daily for 7 days, on a 1-week on, 1-week off schedule. Compounding at the Ontario Veterinary College pharmacy is as follows: The contents of a 3 million IU vial of rhIFN-α (Roferon-A; a recombinant hybrid product containing α A/D subtypes) is diluted in 1 L of normal saline. The resulting solution contains 3000 IU/mL. One-milliliter aliquots can be frozen for several months. To dispense, 1 mL of the 3000 IU/mL solution is diluted to 100 mL with saline, yielding a 30 IU/mL solution. The stability of this solution is not known; we dispense only enough for 1 month (slightly modified from Weiss et al. [1991], as the stability of the dilutions is unknown). The optimum dose of other recombinant and natural hIFNs is unknown, but likely different.

Controlled clinical trials in spontaneously occurring retroviral infections need to be designed and performed. On a purely anecdotal basis, our experience in treating a limited number of cats with FeLV or FIV infections suggests that clinical benefit is associated with oral interferon therapy and that it is safe and inexpensive.

Interferons as Therapy for Cancer

Interferons inhibit cell proliferation of both normal and malignant cells and have numerous immunomodulating effects. Several human cancers respond to IFN therapy. At present, there are only preclinical data suggesting that IFNs may have some utility in the treatment of cancer in companion animals. When canine mammary tumor and melanoma cell lines were incubated with canine IFN-γ, significantly increased expression of major histocompatibility antigen class I and II antigens and tumor-associated antigens were observed. Increased expression of these antigens (Schijns et al., 1995b) may be of benefit in tumor cell recognition and rejection by the immune system. In another study, growth of canine and feline tumors was shown to be inhibited by rhIFN-α and rhIFN-γ in vitro. Sensitivity to IFN varied according to the type of neoplasm, with round cell tumors being most sensitive (Kessler et al., 1996). Recombinant rfeIFN was found to have a dose-dependent inhibitory effect on cell growth and colony formation on cell lines derived from canine acanthomatous epulis, benign mixed mammary tumor, squamous cell carcinoma, and malignant melanoma.

INTERLEUKINS

Interleukin Biology

There are currently 17 defined ILs, named in order of discovery and classified into groups based on structure, function, or both. ILs are a diverse group of cytokines, with functions including enhancement or suppression of various cells of the immune system (e.g., IL-1, IL-2, IL-4, IL-9, IL-10, IL-12, IL-13, IL-17), hematopoietic growth factor activity (e.g., IL-3, IL-11, IL-17), and the regulation of leukocyte function (e.g., IL-5 modulates eosinophil function; IL-8 is chemotactic for neutrophils). Some are growth factors for cells of the immune system (e.g., IL-7, IL-11, IL-14, IL-15), whereas others enhance the acute phase response (e.g., IL-1, IL-6). Most interleukins have multiple effects on various cells and are part of complex regulatory cascades. Depending on the specific interleukin, they are produced by T and B lymphocytes, macrophages, fibroblasts, and other stromal cells.

Examples of Interleukin Therapy in Dogs and Cats

Interleukin-1

Human rIL-1α was shown to be chemokinetic and chemotactic for canine neutrophils in vitro and to cause dose-dependent and selective neutrophil infiltration after intradermal administration (Thomsen and Thomsen, 1990). The pharmacokinetics of a single dose of human IL-1 has been studied in the dog. Interleukin-1 was rapidly distributed, with a volume of distribution approximately twice that of the total body water of a lean dog. The terminal half-life was less than 30 minutes. Within approximately 1 hour after dosing (Gray et al., 1993), IL levels were below the quantifiable limit of the ELISA assay. As IL-1 is a central mediator of inflammation, these data are useful for studying the physiology of IL-1; however, pharmacologic efforts will focus on inhibition of IL-1 activity, with applications in the therapy of acute and chronic inflammatory disorders and septic shock.

Interleukin-2

Interleukin-2 synthesis is triggered by antigen-induced activation of T lymphocytes, and its most important activity is the promotion of clonal expansion of antigen-specific T cells. In NK cells and macrophages, IL-2 also promotes proliferation, production of IFN-γ, and cytolytic activity. It also induces growth of B cells as well as immunoglobulin secretion. An important clinical consideration is the observation that NK cells cultured in the presence of IL-2 have enhanced cytotoxic activity, with increased capability for lysis of neoplastic cells. These activated cells are called *lymphokine-activated killer* (LAK) cells. Interleukin-2 is thus an attractive agent for the therapy of neoplastic disorders; however, parenteral administration of IL-2 is associated with significant toxicity, which is due to the secondary release of IL-1, IFN-γ, IL-6, and TNF-α1.

Interleukin-2 was licensed in the United States in 1992 for the treatment of metastatic renal cell cancer, becoming the first biologic agent approved for treatment of any cancer in humans. The availability of recombinant IL-2 spurred the development of "adoptive immunotherapy," which refers to the transfer to the tumor-bearing patient immune cells that mediate antitumor effects. Adoptive immunotherapy has been performed with LAK cells and tumor-infiltrating lymphocytes. Interleukin-2 is necessary for the generation of these cells in vitro and in vivo and is also administered systemically along with these cells in an effort to keep them functioning in the patient. More recently, IL-2 gene therapy for various cancers has been developed.

Several in vitro studies have demonstrated that rhIL-2 has activity in companion animals similar to the activity recognized in humans. Feline lymphocytes responded appropriately to the cytokinetic action of systemically administered rhIL-2 (Gonsalves et al., 1991), and adoptive immunotherapy of FeLV-infected cats with lectin/rhIL-2-activated lymphocytes, IFN-α, and AZT led to reconstitution of antiviral humoral immunity, counteracted immunosuppression, and induced the reversal of retroviremia (Fox et al., 1994). Feline IL-2 cDNA was cloned, and the recombinant protein was shown to promote proliferation of feline, but not human, cells (Cozzi et al., 1993, 1995). Helfand et al. (1992) demonstrated that the immunobiology of IL-2 in the dog is similar to that of humans. Tumor cytotoxicity was induced in vitro in canine lymphocytes with rhIL-2, demonstrating that functional and morphologic changes compatible with LAK cells could be obtained in dogs (Helfand et al., 1994c; Mitchell et al., 1991; Raskin et al., 1991). In other experiments, monoclonal antibodies reactive with GD2 and GD3 disialogangliosides expressed on canine malignant melanoma cells were shown to trigger increased tumor killing when cultured with rhIL-2-activated peripheral blood lymphocytes (Helfand et al., 1994a).

Infusion of rhIL-2 into normal dogs resulted in lymphocytosis and enhanced in vitro lysis of a canine tumor cell line. Side effects included vomiting, diarrhea, and inactivity (Helfand et al., 1994b). Recombinant human TNF and rhIL-2 were administered in a sequential schedule to 30 dogs with a variety of spontaneous neoplasms. Objective tumor responses were seen in dogs with oral melanomas and cutaneous mast cell tumors. Dose-limiting toxicities were primarily gastrointestinal (Moore et al., 1991).

In an effort to develop a delivery system that would be associated with less toxicity, Khanna and coworkers nebulized free rhIL-2 and rhIL-2–containing liposomes into normal dogs. Free IL-2 resulted in increased peripheral blood mononuclear cell activation compared with saline-treated control dogs. Interleukin-2 liposomes resulted in significantly increased bronchoalveolar lavage (BAL) effector leukocyte numbers and activation compared with empty liposomes. Toxicity was not recognized with either IL-2 preparation. The authors suggest that nontoxic activation of pulmonary immune effectors for the treatment of lung cancer may be possible using nebulized IL-2 liposomes (Khanna et al., 1996b). In dogs with primary and metastatic lung cancer, nebulized IL increased the total number of BAL macrophages, eosinophils, and lymphocytes compared with pretreatment levels, and there was increased expression of CD3 on BAL lymphocytes. The relative expression of CD4 and CD8 remained unchanged during the study. Mean BAL cytolytic activity increased compared with pretreatment activity during therapy to a maximum at 15 days, and then it decreased (despite continued aerosol therapy) to pretreatment levels at day 30. Antibodies reacting with hIL-2 developed in the serum of all treated dogs, possibly accounting for the decrease in BAL cytolytic activity at day 30 compared with day 15. Complete regression of pulmonary metastases in two of five dogs with metastatic osteosarcoma was maintained at greater than 370 and 700 days (Khanna et al., 1996a).

Gene therapy with IL-2 has also been reported in dogs. Quintincolonna et al. (1996) reported that dogs with oral melanoma treated with local resection, 45-Gy radiation therapy, and repeated local injections of xenogeneic Vero cells transfected with an hIL-2–expressing plasmid had longer median survival times than did dogs treated with resection and radiation therapy alone; dogs treated with surgery, radiation therapy, and nonengineered Vero cells; or dogs treated with surgery, radiation therapy, and injection of rhIL-2 into the tumor bed. Similar results were seen in cats with fibrosarcomas. An unexpected observation was the development of metastatic fibrosarcoma in three of five cats that relapsed in the group treated with engineered cells. Complications seen in some dogs and cats included anaphylaxis associated with injection of Vero cells and local inflammatory reactions (Quintincolonna et al., 1996).

We have been using a replication-incompetent adenovirus to deliver rhIL-2 cDNA to various feline and canine solid tumors. In vitro experiments have shown that the adenovirus vector is highly infective for canine cells and that IL-2 expression occurs at high levels for at least 2 weeks. In a limited number of cases, we have seen dramatic and durable remission of melanoma metastatic to the lung. Clinically significant IL-2 toxicosis, including fever, inappetence, hypotension, and noncardiogenic pulmonary edema, has occurred in dogs and cats treated with this system.

Canine IL-2 cDNA has been cloned, but is not commercially available (Dunham et al., 1995; Knapp et al., 1995).

Other Interleukins

Interleukin-6 is a proinflammatory cytokine (along with IL-1 and TNF-α) with pleiotropic activity, including effects on B and T cells and induction of acute phase proteins. Elevated levels of IL-6 have been reported in Sharpei dogs with recurrent febrile illnesses, and IL-6 dysregulation has been postulated to play an etiologic role in the syndrome (Rivas et al., 1992). Dogs with juvenile polyarteritis syndrome were also found to have increased levels of serum IL-6 activity during acute illness, but undetectable levels during convalescence. Treatment of acutely ill dogs with prednisone resulted in rapid clinical improvement accompanied by a decrease in IL-6 activity; withdrawal of prednisone resulted in reappearance of signs and high serum IL-6 activity. Clinically, the most important inhibitors of IL-6 expression are glucocorticoids (Hogenesch et al., 1995). Interleukin-6 also has marked effects on megakaryocyte and platelet physiology. In dogs, 80 μg/kg per day rhIL-6 increased platelet counts modestly and enhanced the sensitivity of platelets to activation in response to thrombin and platelet-activating factor (Peng et al., 1994). Other investigators have shown that IL-6 promoted increases in plasma fibrinogen and von Willebrand factor and a decrease in free protein S concentrations. These effects on the clotting mechanism may result in an overall prohemostatic tendency, which may prove beneficial for the amelioration of bleeding associated with a variety of conditions. Additional investigation is required to determine if IL-6–mediated alterations of hemostasis may lead to pathologic thrombosis (Burstein, 1994).

The cDNA for feline IL-6 has been cloned, and the recombinant protein has been described (Bradley et al., 1993; Ohashi et al., 1993).

Interleukin-11 is a pleiotropic cytokine that enhances the activity of primitive, erythroid, and megakaryocyte progenitor cells and the production of hepatic acute phase proteins, and it supports growth of the intestinal epithelium. In animal models, rhIL-11 has been shown to be effective in reconstituting platelet levels after the administration of chemotherapy or radiation therapy and in protection against radiation or drug-induced damage to the intestinal epithelium. Clinically, rhIL-11 has been used to support platelet levels in human cancer patients and in the management of Crohn's disease and ulcerative colitis. A side effect that limits the administration of rhIL-11 is plasma volume expansion, resulting in edema, a fall in hematocrit, and cardiac arrhythmias. In dogs, rhIL-11 increased platelet counts, platelet size, ploidy, number of megakaryocytes, and marrow and peripheral blood. Pneumonitis may be a dose-limiting side effect in dogs (Nash et al., 1995b).

HEMATOPOIETIC GROWTH FACTORS

In humans, the hematopoietic system produces in the order of 10^{11} cells daily and is able to rapidly increase production even further when stimulated by hematopoietic growth factors. Hematopoietic growth factors include erythropoietin (EPO), granulocyte colony-stimulating factor (G-CSF), granulocyte/macrophage colony-stimulating factor (GM-CSF), monocyte colony-stimulating factor (M-CSF), thrombopoietin, stem cell factor (SCF), and most of the interleukins. Hematopoietic growth factors act synergistically at various levels in the hematopoietic developmental system, and their actions are rarely restricted to a given lineage. The cDNAs for all of the known human factors, and some of the canine and feline factors, have been cloned. Recombinant hG-CSF (filgrastim), rhGM-CSF (sargramostim), and rhEPO (epoetin) are commercially available. For humans, this has led to significant advances in the management of a variety of hematologic and neoplastic disorders. It is likely that these products, and eventually species-specific growth factor products, will make similar advances possible for companion animals.

Recombinant Human Erythropoietin

In dogs, EPO is secreted by cells adjacent to the proximal convoluted tubules in response to renal hypoxia. Erythropoietin stimulates the proliferation and maturation of erythroid progenitor cells, primarily colony-forming unit erythroid cells. Megakaryocytes are also stimulated by EPO. Recombinant human EPO was the first commercially available hematopoietic growth factor released for clinical use in humans and is indicated for the treatment of anemia secondary to chronic renal failure, anemia secondary to the treatment of human immunodeficiency virus with AZT, and anemia secondary to cancer chemotherapy. The use of rhEPO in small animals is addressed elsewhere in this text (see Chapters 7 and 21).

Growth Factors Affecting Myeloid Lineages

Granulocyte Colony-Stimulating Factor

Granulocyte CSF is produced by fibroblasts and endothelial cells stimulated by IL-1 or TNF and by macrophages stimulated by bacterial endotoxins. Its major effects are on neutrophils and neutrophil progenitors. Recombinant hG-CSF is commercially available and for humans is indicated to decrease the incidence of infection in patients with nonmyeloid malignancies receiving myelosuppressive chemotherapy with or without bone marrow transplantation, congenital neutropenia, and cyclic neutropenia.

In normal dogs, rhG-CSF induces rapid and marked neutrophilia but, similar to the situation with rhEPO, also induces antibodies that react with both rhG-CSF and endogenous canine G-CSF, leading to chronic, but reversible, neutropenia (Hammond et al., 1991; Lothrop et al., 1988). Whether dogs with cancer receiving immunosuppressive chemotherapy are able to mount an immune response to rhG-CSF has not yet been determined. In dogs treated with total body irradiation, rhG-CSF therapy was associated with earlier recovery of neutrophils and platelets and reduced the lethality of the hematopoietic insult compared with untreated irradiated controls (MacVittie et al., 1990). In grey collie dogs with cyclic hematopoiesis, rhG-CSF eliminated neutropenic episodes but did not correct abnormalities in platelet aggregation or serotonin content or decreased neutrophil myeloperoxidase activity (Lothrop et al., 1988; Pratt et al., 1990). Recombinant hG-CSF has also been used to treat drug-induced pancytopenia in a dog (Holland et al., 1996).

Canine G-CSF has been cloned but is not commercially available. In normal dogs, rcG-CSF was shown to induce rapid and marked increases in neutrophils, moderate increases in lymphocyte and monocyte counts, and bone marrow hyperplasia. For example, five normal dogs were given 5 μg/kg rcG-CSF per day subcutaneously for 4 weeks. The mean neutrophil counts increased from 6537/μL to 26,330/μL within 24 hours after the first injection to a maximum of 72,125/μL by day 19. Blood counts returned to normal within 5 days after discontinuation of rcG-CSF, and clinically significant toxicoses were not associated with rcG-CSF administration. The induction of neutrophilia was induced again upon repeated administration (Kurzman et al., 1992; Obradovich et al., 1991; Zinki et al., 1992). Recombinant cG-CSF prevented neutropenia and associated clinical signs in cyclic hematopoietic dogs but did not completely eliminate the cycling of neutrophils in cyclic hematopoietic dogs. Also, the time to bone marrow reconstitution was not decreased in dogs treated with rcG-CSF after autologous bone marrow transplantation, emphasizing that rcG-CSF action depends on the presence of progenitor cells in the bone marrow (Mishu et al., 1992).

To evaluate the utility of rcG-CSF in the management of chemotherapy-induced neutropenia, myelosuppression was induced with mitoxantrone in normal dogs and then treated with daily rcG-CSF for 20 days. None of the dogs receiving rcG-CSF developed serious neutropenia, while four of five untreated dogs did. These findings demonstrate that rcG-CSF is capable of reducing the duration and severity of mitoxantrone-induced myelosuppression (Ogilvie et al., 1992). The optimal cost-effective timing and duration of treatment for the management of therapy-induced myelosuppression has not been determined for canine or human origin cytokines, and it may only be necessary to treat when neutrophil counts fall below 1000 cells/μL, and only a few days of therapy may be necessary (Hammond et al., 1990). In addition to cancer treatment–induced neutropenia, rcG-CSF has been used to accelerate the rate of recovery from neutropenia in dogs with parvovirus. It has not been useful in dogs without neutrophil progenitors, such as those with aplastic anemia secondary to ehrlichia infections or estrogen toxicity (Ogilvie, 1995). Historical and bone marrow evaluations are important in determining which animals are likely to respond to therapy with any hematopoietic growth factor.

Recombinant G-CSFs of both human and canine origin have been studied in normal cats. In one study, 5 μg/kg rcG-CSF per day was administered to healthy cats for 42 days. Mean neutrophil counts increased from 10,966 cells/μL to 30,688 cells/μL within 24 hours after the first dose. Neutrophil counts increased and remained elevated until cytokine administration was discontinued at 42 days. There were no adverse effects reported (Obradovich et al., 1993). Normal cats given rhG-CSF developed neutropenia before the end of 3 weeks of therapy, presumably because antibodies developed against the growth factor (Fulton et al., 1991). Neutropenia has not been observed in cats given rcG-CSF, likely due to greater homology between the cat and dog cytokines (Obradovich et al., 1993). It is not known if cats with immunosuppressive disorders or cats receiving antineoplastic chemotherapy are able to form antibodies that react with human-derived cytokines. Cats with Chediak-Higashi syndrome treated with rcG-CSF had increased neutrophil counts and improvement in neutrophil function (Colgan et al., 1992). Recombinant G-CSF (of any species origin) may also be useful in the management of feline panleukopenia, neutropenia associated with FeLV and FIV infections, and sepsis.

Granulocyte/Macrophage Colony-Stimulating Factor

Granulocyte/macrophage CSF is produced by the bone marrow stroma and T and B cells and is a regulator of the intermediate stages of hematopoiesis. It supports the expansion and growth of both granulocytic and macrophage lineages as well as enhancing the function of mature macrophages and neutrophils (Vose and Armitage, 1995). In humans, rhGM-CSF is indicated for the acceleration of hematopoietic reconstitution after autologous bone marrow transplantation in lymphoproliferative disorders. Recombinant hGM-CSF induces leukocytosis (primarily neutrophils, but also eosinophils and monocytes) in normal dogs. In dogs undergoing total body irradiation and supported with rhGM-CSF, there was decreased severity and shortened duration of neutropenia, indicating that rhGM-CSF can be effective monotherapy for radiation-induced bone marrow failure in dogs. Anti–rhGM-CSF antibodies developed in 1 to 2 weeks, and persisted for at least 150 days. Another potential concern with rhGM-CSF is that platelet counts dropped to nadirs of 20% to 30% normal levels (Mayer et al., 1990; Northdurft et al., 1992).

Canine GM-CSF has been cloned and its activity investigated in normal dogs, where it induced significant increases in neutrophil and monocyte levels. As with the human recombinant product, mean platelet counts decreased significantly. Further investigation into the mechanism of thrombocytopenia suggested that GM-CSF activates hepatic macrophages, with resultant increases in phagocytosis of platelets (Nash et al., 1991, 1995a). After otherwise lethal total body irradiation, rcGM-CSF was not effective in promoting hematopoietic recovery or improving survival, suggesting that in situations of severely limited stem cell response, G-CSF may be more effective than GM-CSF in eliciting a rapid neutrophil recovery (Nash et al., 1994).

In an effort to avoid daily systemic administration of recombinant GM-CSF, we are investigating hematopoietic cytokine gene transfer to the marrow cavity of normal dogs by direct intramarrow injection of adenoviral vector–cGM-CSF constructs (AdcGM-CSF). Replication-deficient adenoviral vectors efficiently transduce marrow stromal cells and induce high levels of cytokine production. In vivo, high levels of protein production are found in bone marrow aspirates 72 hours after direct intramarrow administration of AdcGM-CSF. Localized myeloid expansion of marrow and significant peripheral leukocytosis have been identified in all treated dogs, and peripheral blood changes last for up to 3 weeks after a single intramarrow injection. It appears that adenoviral-mediated cytokine expression from the marrow of a single large bone (ileum) leads to compartmentalized expression of GM-CSF and an increase in hematopoiesis. We are currently evaluating this approach in otherwise normal dogs made neutropenic with mitoxantrone.

GM-CSF is a mediator of antibody-dependent cellular cytotoxicity and increases major histocompatibility complex expression, giving GM-CSF potential utility as a modulator of antitumor immunity. A vaccine consisting of irradiated hGM-CSF transfected canine melanoma cell line has been reported to produce GM-CSF at the site of intradermal injection for extended periods of time in normal dogs. A Phase I clinical trail using autologous tumor cells in dogs with melanoma and soft tissue sarcomas has been initiated (Hogge et al., 1996).

Other Hematopoietic Growth Factors Not Yet Available for Clinical Use

Stem cell factor (SCF: c-kit ligand, mast cell growth factor) is produced primarily by bone marrow stroma, with effects on a wide range of precursor cells at different stages of differentiation, including primitive hematopoietic stem cells. It has little activity as a single agent; however, it is a potent co-stimulatory molecule when administered in combination with other hematopoietic growth factors. Canine SCF cDNA has been cloned and studied in long-term bone marrow cultures. Alone, rcSCF was nonstimulatory for committed marrow precursors. Synergistic stimulation of granulocyte/macrophage colony-forming units was demonstrated between rcSCF, rhGM-CSF, and rhIL-6 (Khanna et al., 1996a). In vivo, rcSCF induced neutrophilia in normal dogs and supported hematopoietic recovery in normal dogs undergoing total body irradiation without marrow transplant; however, results were similar to those obtained with rcG-CSF (Schuening et al., 1993). Recombinant canine SCF also prevented neutropenic periods in grey collie dogs with cyclic hematopoiesis (Dale et al., 1995).

Recombinant human IL-3 and piXY321 (a recombinant fusion protein of GM-CSF and IL-3) have not shown clinical utility in a limited number of animals (Ogilvie, 1995). M-CSF, IL-1, and other hematologic growth factors have not been evaluated in dogs and cats. In summary, the current situation is that rhEPO and rhG-CSF are commercially available but expensive, are well tolerated, and have great potential for improving the management of dogs and cats with chronic renal failure and iatrogenic myelosuppression.

LIPOSOMAL PRODUCTS

Liposomes are microscopic closed vesicles consisting of aqueous compartments separated from the environment by concentric phospholipid bilayers. The in vivo distribution of a liposome preparation is strongly influenced by its physical characteristics. Properties that can be controlled during manufacture include membrane charge and stability (which are determined by choice of lipid composition) and liposome size (which is determined by the method of preparation). Liposomes are biodegradable, nontoxic, and in themselves immunologically inert. After phagocytosis by macrophages, liposomes are digested by lysosomal phospholipases. The utility of liposomes lies in their ability to be "loaded" with biologic response modifiers, drugs, or antigens, injected intravenously, and phagocytosed by selected cell populations. In the context of companion animal medicine, liposome preparations have been used primarily to activate macrophages in an attempt to increase killing of various cancers. More recently, systems designed to deliver chemotherapeutic drugs to various cancers have been reported.

Muramyl dipeptide (MDP: a bacterial cell wall component) and its derivative muramyl tripeptide (MTP) are efficient macrophage activators. In vivo, they are rapidly cleared after parenteral injection. If liposomes are used to carry and deliver them to macrophages, however, enhanced macrophage activity is developed against malignant cells. Activated macrophages selectively lyse neoplastic cells and do not affect non-neoplastic cells. In vitro studies suggest that macrophage killing does not depend on immunologic recognition or activity.

MacEwen et al. (1989) have reported several studies investigating the use of liposome biologic response modifier systems in cancer-bearing dogs. Muramyl tripeptide–phosphatidylethanolamine (MTP-PE) is a synthetic derivative of MDP with enhanced plasma half-life and reduced toxicity. Administration of liposome-encapsulated MTP-PE (L–MTP-PE) increased monocyte tumoricidal activity; increased levels of β-microglobulin, TNF-α, IL-6, neopterin, ceruloplasmin, and C-reactive protein; and upregulated IL-1 (Kurzman et al., 1993; Shi et al., 1995). In an in vitro cytotoxicity assay, normal dogs treated intravenously with L–MTP-PE had enhanced killing of canine osteosarcoma cell line D-17 and human melanoma cells (Smith et al., 1993). L–MTP-PE was well tolerated, with the only side effect being a mild increase in body temperature 2 to 4 hours after administration (MacEwen and Kurzman, 1996). Treating normal dogs with rcG-CSF before L–MTP-PE administration led to increased monocyte counts and enhanced levels of serum TNF-α activity compared with dogs treated with L–MTP-PE alone, suggesting that the combined use of colony-stimulating factors and effector cell activators may be useful in treating some cancers (Kurzman et al., 1994).

The results of several clinical trials evaluating the utility of L–MTP-PE in dogs with appendicular osteosarcoma have been published. In the initial trial, dogs treated with L–MTP-PE after amputation (chemotherapy was not administered to either group) had significantly increased survival times compared with untreated amputated controls (MacEwen et al., 1989). In a follow-up study, 40 dogs with appendicular osteosarcoma were treated with amputation and cisplatin chemotherapy. After completion of chemotherapy, dogs without evidence of overt metastatic disease were treated with either L–MTP-PE or liposome placebo. The L–MTP-PE group had significantly longer survival times (MacEwen et al., 1989) (median 14.4 months) than did the placebo group (median 9.8 months) (Kurzman et al., 1995). A third trial evaluated the efficacy of L–MTP-PE given concurrently with cisplatin after amputation. There was no significant difference between the group receiving L–MTP-PE once weekly, the group receiving it twice weekly, or the group receiving liposome placebo (Kurzman et al., 1995). These studies suggest that L–MTP-PE has clinically significant antitumor activity in dogs with appendicular osteosarcoma when given as a single agent after amputation or amputation plus cisplatin chemotherapy; however, this effect is lost when L–MTP-PE is given concurrently with cisplatin. It is possible that the failure of concurrent therapy was associated with the choice of chemotherapeutic drug. Drugs such as doxorubicin have been shown to enhance macrophage cytotoxicity in dogs and may be a better choice for combination therapy (Shi et al., 1993).

The efficacy of L–MTP-PE was also evaluated in dogs with splenic hemangiosarcoma. After splenectomy, dogs were randomized to receive either cyclophosphamide plus doxorubicin chemotherapy with concurrent L–MTP-PE or liposome placebo. Dogs treated with L–MTP-PE had increased serum TNF-α and IL-6 activities and significantly prolonged disease-free intervals and overall survival times compared with the placebo liposome group (Vail et al., 1995).

Intravenous L–MTP-PE has also been shown to induce increased serum TNF-α and IL-6 activities when administered to normal cats (Fox et al., 1994). Forty cats with mammary gland adenocarcinoma were treated with radical mastectomy followed by L–MTP-PE or placebo in a double blind study. Unfortunately, there were no differences in either disease-free interval or survival between the two groups (Fox et al., 1995).

As noted, conventional liposomes are rapidly cleared by macrophages after intravenous injection, which is appropriate for activation of macrophages or antigen presentation. Recently, it has been shown that the inclusion of GM1 ganglioside phosphatidylinositol, cerebroside sulfate, and polyethylene glycol (PEG) within the liposome biolayer can prolong liposome circulation time, decrease liposome content leakage, and decrease uptake by macrophages. Liposomes with this type of formulation and kinetics are termed *sterically stabilized* (Stealth liposome is a registered trademark of a sterically stabilized liposome formulation.) Inhibition of the rapid uptake of liposomes by the macrophage/monocyte system and reduction of the rate of drug leakage have led to the development of long-circulating liposomal drug delivery systems. Sterically stabilized liposomes are highly concentrated in skin, followed by liver and spleen, and tumors. Liposome localization in tumors appears to be the result of enhanced rate of extravasation through abnormally permeable microvasculature coupled with impaired lymphatic drainage (Gabizon et al., 1997; Papahadjopoulos and Gabizon, 1995).

Doxorubicin encapsulated in PEG-coated liposomes has an extremely long half-life, slow clearance, and small volume of distribution. A Phase I dose-escalation study with pegylated liposomal doxorubicin was performed in tumor-bearing dogs. The maximally tolerated dose was 1.0 mg/kg IV every 3 weeks, and cutaneous toxicity was dose limiting. Significant myelosuppression did not occur (Vail et al., 1997). A clinical trial in which immunoliposomes consisting of Stealth liposomal doxorubicin covalently linked to monoclonal antibody 231 (which recognizes and binds to an internalizing surface epitope expressed on lymphoma cells) was recently proposed (Allen et al., 1996).

Sterically stabilized liposome systems will be developed to reduce toxicity and increase efficacy of other drugs. For instance, a Stealth liposome-encapsulated cisplatin preparation is undergoing preliminary testing in cats, which are notably sensitive to the toxic effects of cisplatin (Thamm and Vail, 1996).

EXAMPLES OF BIOLOGIC RESPONSE MODIFIERS LICENSED FOR USE IN DOGS AND CATS

Although the cDNAs for many dog and cat cytokines have been cloned, there are no canine or feline species-specific cytokines currently marketed in North America. As discussed earlier, recombinant human cytokines often have dramatic effects in companion animals, and, although the induction of antirecombinant human cytokine antibodies is a concern, their significance may depend on the clinical situation (e.g., they are significant in animals receiving rhEPO but may not be significant when rhG-CSF is given to neutropenic animals for a short period after chemotherapy).

Two cytokine-inducing agents are licensed for the treatment of neoplasia in dogs and cats. Convincing clinical trails have not been reported for either; however, the rationale for their use seems reasonable when other treatment modalities are not options.

SUMMARY

The concept of enhancing the normal immune response against infections and neoplasms has been considered for decades. The administration of various natural and synthetic products to simulate systemic infections has largely given over to the idea that specific cytokines can be used effectively when administered systemically. Interferons, interleukins, and hematopoietic growth factors may offer substantial clinical benefit in chronic viral infections and in cancers such as osteosarcoma, melanoma, and lymphosarcoma. Erythropoietin has been shown to have great utility in the management of chronic renal failure. At this point, only recombinant products derived from humans are commercially available, and they are expensive and not licensed for use in companion animals. Nevertheless, these products may have significant clinical impact on several highly fatal disorders of dogs and cats. When administered systemically, cytokines perturb complex regulatory pathways, and serious side effects may occur. Innovative delivery methods, such as liposomes, gene therapy, and even oral administration, may increase the therapeutic index of these molecules. Biologic response modification, cytokine biology, and associated delivery systems are rapidly changing fields, and the small animal veterinarian will need to watch for significant advances in these areas over the next several years.

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21

Recombinant Biotechnology in Veterinary Therapeutics

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- INTRODUCTION
  - Biotechnology and Genetic Engineering
  - Client Acceptance
- FUNDAMENTALS OF BIOTECHNOLOGY
  - Basic Cellular Processes
    - Replication
    - Transcription
    - Translation
  - Molecular Biology Tools
  - Production of Recombinant Products
- RECOMBINANT PRODUCTS
  - Principles of Protein or Peptide Drug Therapy
    - Absorption, Distribution, and Mechanisms of Degradation
    - Drug Delivery
    - Immunogenicity
  - Hematopoietic Growth Factors
    - Recombinant Human Erythropoietin
    - Recombinant Human and Recombinant Canine Granulocyte Colony-Stimulating Factor
    - Recombinant Human and Recombinant Canine Granulocyte-Macrophage Colony-Stimulating Factor
    - Other Hematopoietic Growth Factors
  - Hormone Therapy
    - Recombinant Human Insulin
    - Growth Hormone
  - Immune Modulators
    - Recombinant Human Interferon-α2A
    - Recombinant Human Tumor Necrosis Factor-α and Recombinant Human Interleukin-2
  - Vaccine Technology
  - Monoclonal Antibodies
- FUTURE DIRECTIONS IN GENE THERAPY

INTRODUCTION

Since the deduction of the double helical structure of deoxyribonucleic acid (DNA) by Watson and Crick in 1953, steady progress has been made in elucidation of the form, function, and regulation of DNA, ribonucleic acid (RNA), and protein. Application of molecular biology advances to the applied environment of clinical medicine, including pharmacology, began in the late 1970s. The purpose of this discussion is to briefly review the principles of molecular biology necessary for understanding technologic advances in pharmacology and to highlight products of significance to veterinary medicine. A detailed understanding of product production processes is not necessary for the practitioner, but an appreciation of cellular and molecular principles is important for adequate client communication. More than most pharmaceuticals, recombinant products have engendered debate and concerns that must be understood and dealt with by medical professionals.

Biotechnology and Genetic Engineering

Biotechnology is best defined as the application of biologic organisms, systems, or processes to manufacturing and service industries (Headon, 1994). Manipulation of genetic elements that results in alteration to protein or in changes in patterns of protein expression is termed *genetic engineering* or *recombinant technology*. Biotechnology is a science that has been used for thousands of years to produce fermentation products such as beer, wine, yogurt, and cheese. In more recent history, microorganisms have been used to produce compounds such as antibiotics, vitamins, and amino acids (Demain and Soomon, 1981). Improved function and efficiency of the microbes used in biotechnologic processes have been achieved by organism selection or natural mutation. With the availability of molecular biologic tools, production efficiency has been enhanced by genetically engineering desirable production traits into biotechnologic systems.

Similarly, development of more efficient, high-yielding animals and plants was once limited to selection and long-term breeding programs. Although selection and mutation remain important tools, genetic engineering facilitates construction of organisms capable of producing a higher quality and quantity of product. Transgenic animals offer the prospect of increased disease resistance, improved metabolic processing of nutrients, increased growth potential, and in vivo production of useful compounds in natural secretions such as milk (Ward and Nancarrow, 1991; Pinkert, 1994). With the promise of genetic engineering, however, have come many obstacles, especially when the technology is applied to complex mammalian systems. For example, animals expressing a growth hormone transgene grow larger but also suffer from an array of problems related to overproduction of the hormone (Hammer et al., 1985). Understanding and manipulating the behavior of transgenes will have important pharmacologic and molecular therapeutic implications.

Genetic engineering and biotechnology offer many advantages to the medicinal and pharmaceutical chemistry industry. First, a wide range of biologic substances, including many immunologically active factors, may now be produced in quantities sufficient to test their clinical efficacy. Innovative therapies for cancer, immunologic disorders, inflammatory diseases, and others have occurred through increased availability and testing of new biologic substances. A second and related advantage is that biologic substances, once available in only small amounts from tissue extraction, are now produced more economically and with higher quality. Preparation of recombinant products has decreased the risk of patient contamination with human or animal viruses derived during tissue extraction. For example, since 1992, hemophiliacs requiring factor VIII utilize a recombinant product free of potential contamination with human immundeficiency virus (HIV) (Schwartz et al., 1990).

Recombinant technology has also been used to improve the economy of production of existing therapeutic agents. In production of antibiotics, the extent of product formation is often determined by rate-limiting enzymatic reactions. Supplementation of the reaction with recombinant reagents can increase the productivity of the organism and the antibiotic yield. Of particular importance to veterinary medicine is the potential for genetic engineering and biotechnology to yield useful recombinant vaccines for the prevention of viral, bacterial, and parasitic diseases. Development of new vaccines is among the most active areas in veterinary biotechnology (Yilma, 1994).

Finally, biotechnologic advances have led to an increased understanding of fundamental properties of genes and proteins. Acquisition of sequence information through genome mapping coupled with major strides in protein crystallography have led to enhanced understanding of individual proteins. Armed with detailed information on proteins, pharmacologists and synthetic chemists have been successful in developing a number of important drugs. As a recent example, antiviral protease inhibitors have become available that, when used in combination with other drugs, hold great promise for the treatment of HIV and possibly other retroviral diseases (Cohen, 1996). These and other drugs could not have been developed as rapidly or as effectively without the knowledge gained from molecular biologic studies.

Client Acceptance

Biotechnology has engendered controversy centered on at least three issues that may be of concern to clients. The first is opposition to the use of animals in biomedical research. Animal rights activists defend the position that animal rights are equivalent to human rights and that causing animal discomfort or suffering is impermissible no matter what the gains to society. Alternatively, proponents of animal welfare support the humane, conscientious use of animals in research if an experiment or study is well-justified and peer reviewed and limits the use of animals to the smallest feasible number within the design of the study. In many ways, molecular biology advances have helped to decrease animal use by providing an array of in vitro testing and production systems that utilize prokaryotes rather than eukaryotes. For example, pharmaceutical and cosmetic companies have been criticized for the numbers of animals used in toxicologic testing of certain products. Over the past several years, companies have made an effort to reduce the number of animals used and to rely more heavily on in vitro assessments.

The second issue of concern to some clients may be the idea that scientists are overstepping ethical boundaries by manipulating genetic material and creating novel recombinant organisms. Products that result from these processes may, therefore, be objectionable. In practice, most clients are not aware that a given product has a recombinant origin unless the product has received attention in the popular press (e.g., bovine somatotropin or growth hormone [bST]). In the future, gene therapy and the production of large numbers of transgenic animals will likely engender greater ethical debate with regard to the negative aspects of genetic engineering. Although these areas are currently limited to veterinary research venues, clinical gene therapy trials with humans are ongoing. Regardless of the product or procedure, it is not the veterinarian's role to make ethical judgments for the client. Rather, the practitioner should be prepared to provide clear explanations of recombinant technology that help the client understand the scientific origins of the product or procedure in question.

A final issue, and perhaps the most practical, is client concern over the safety of recombinant products. Most clients are unfamiliar with principles of molecular biology and therefore may be confused about the potential for recombinant products to cause harm. This is an immediate concern in food animal medicine because recombinant products such as bST have already been approved and are in widespread use. In the case of bST, consumers worried that the recombinant bovine hormone could somehow cause hormonal changes in humans who consume bST-containing meat. Multiple studies (Juskevich and Guyer, 1990; NIH Technology Assessment Conference, 1991) have shown this to be false, but many consumers remain wary of the effects of genetically engineered products, especially hormones, in the food chain. Although small animal owners will have somewhat different concerns, they may also express reservations about the potential for recombinant products to cause unexpected effects or revert to "mutant" forms. The same types of concerns were expressed in 1798 when Edward Jenner introduced what was then the very latest in medical technology, vaccination (Moss, 1991). An English engraving from 1802 (Fig. 21–1) suggests that many patients immunized against smallpox feared the emergence of bovine qualities related to the cowpox-derived vaccine. As with immunization, the concept of recombinant technology is becoming less alarming largely as a result of client education. As a health professional, the veterinarian should have an understanding of fundamental cell and molecular biologic principles in order to adequately respond to client concerns or questions.

FUNDAMENTALS OF BIOTECHNOLOGY

The structure of DNA contained in every cell in every living thing is fundamentally the same. This similarity among diverse kinds of organisms makes it possible to take genetic material from one species and recombine it with genetic material from another species. The conservation of genetic processes employed by bacterial and viral cells and those of higher organisms has allowed scientists to construct unique genetic molecules. Understanding how genetic elements are manipulated to produce recombinant drugs and vaccines requires familiarity with selected molecular biologic tools and procedures and with funda-

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Figure 21–1. English engraving by James Gilray (1802) (see Moss, 1991) suggesting that many patients feared the "wonderful effects of the new (smallpox) inoculation" procedure.

mental genetic processes in the cell (Lodish et al., 1995) (Fig. 21–2).

Basic Cellular Processes

Replication

Replication is the process by which strands of DNA are copied into exact copies during cell division. Replication allows the transfer of genetic information to subsequent generations of cells. Two strands of a DNA double helix uncoil through the action of several proteins and enzymes. With the uncoiled strands as templates, two complementary strands are formed by DNA polymerase-catalyzed pairing of new bases with template bases (thymine with adenine, cytosine with guanine). Elongation of each new DNA strand occurs in the 5′ to 3′ direction. The net result is two DNA molecules, each identical to the original double helix.

The details of replication and the rate of the process depend on the complexity and type of parent organism. Some prokaryotic cells replicate their DNA and divide in less than half an hour. Selected strains of *Escherichia coli* bacteria have been chosen by many scientists for development of recombinant products because the molecular biology of this microorganism is well characterized. *E. coli* cells contain a single bacterial chromosome unbounded by a nuclear membrane. The 4 million bases of this chromosome may be replicated in as little as 20 to 30 minutes. All bacterial strains commonly used in production of recombinant pharmaceuticals are deemed safe and have been developed to prevent the escape of recombinant tools into an environment where their effects might not be predictable. "Safe" bacteria were originally designed to preclude replication and growth in mammalian systems by imposing metabolic requirements for substances not present in the human gastrointestinal tract or by selecting for fragile cell walls that burst in the presence of any detergent or low salt concentration. The National Institutes of Health have developed regulatory guidelines for "safe" systems that allow classification of strains and organisms for recombinant use.

Transcription

Transcription (Fig. 21–2B), the second fundamental process to be considered, is similar to replication in that DNA provides a template for construction of a new nucleic acid molecule, this time RNA. A partially unwound section of DNA double helix is recognized by the enzyme RNA polymerase. The unwound section begins and ends at specific, well-defined points and constitutes a transcriptional unit or gene. RNA polymerase catalyzes template-directed addition of nucleotide bases to form a growing transcript (with uracil, not thymine, complementing adenine). The pre-messenger RNA (pre-mRNA) transcript produced is

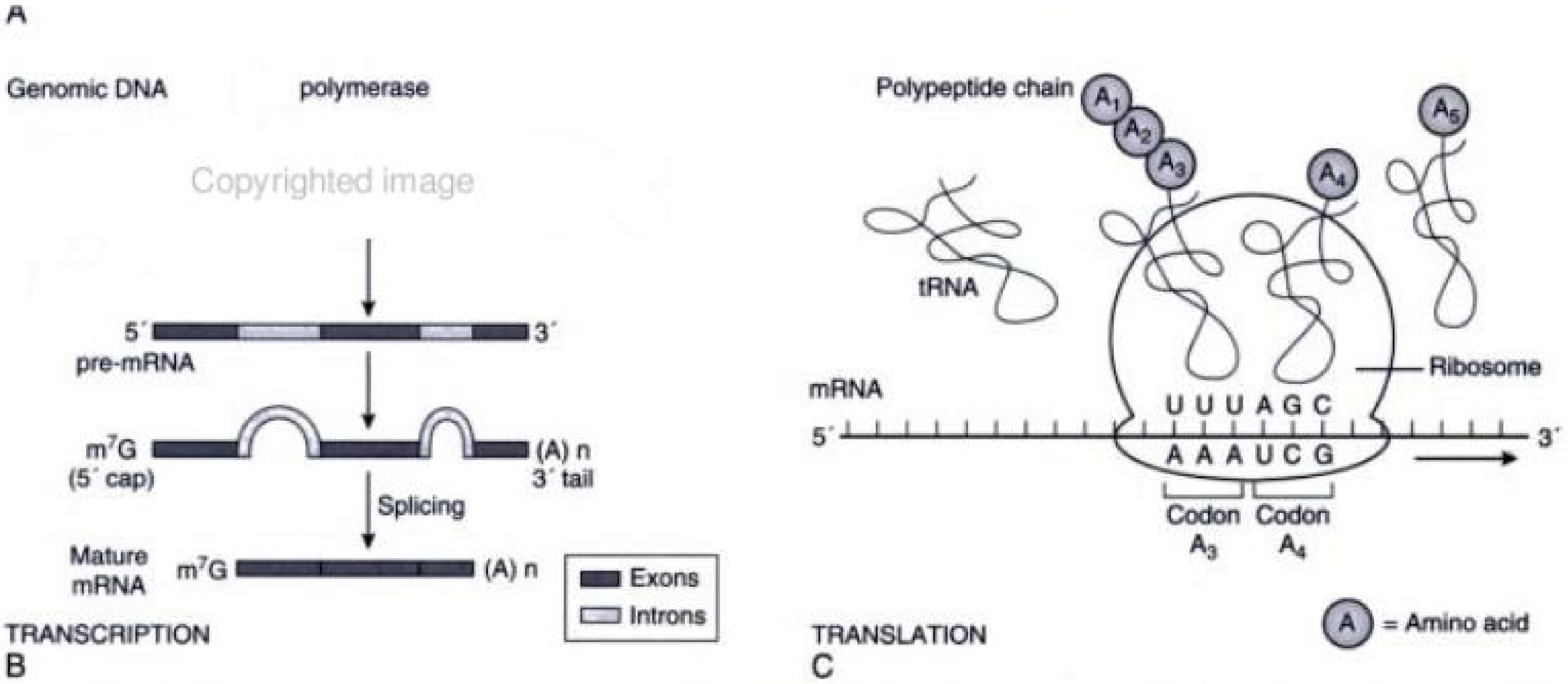

Figure 21–2. Schematic depiction of selected mammalian cell processes. *A*, An overview of the three major genetic processes (replication, transcription, and translation) and of the pathway for secretion of a protein. *B*, A detail of the boxed area in *A* describing the process of transcription and mRNA processing. *C*, A detail of the boxed area in *A* describing the process of translation.

uninterrupted and single stranded. Eukaryotic pre-mRNA is modified in the nucleus by a 7-methyl-guanylate "cap" on the 5′ end, a 3′ poly A tail, and removal or splicing of sequences that correspond to introns in the DNA. Introns are sequences of DNA that do not code for protein, and exons are coding sequences that are ultimately expressed in the RNA transcript and protein product. Following these modifications, mature mRNA then travels to the cytoplasm, where the genetic code is translated to manufacture a specific protein.

Prokaryotic transcription is very similar to the eukaryotic process but is simpler. In bacterial DNA, genes are closely packed with very few gaps, and the DNA is transcribed directly into mature, co-linear RNA. Prokaryotic mRNA may be actively translated into protein while later stretches of the RNA are still being transcribed.

Translation

Translation (Fig. 21–2C) depends on the presence of mRNA, ribosomes (and ribosomal RNA), transfer RNA (tRNA), and appropriate protein factors and enzymes in the cytoplasm of the cell or bacteria. Ribosomes provide the physical site for translation of the mRNA code into protein. Each "word" in the message is specified by a three base pair codon on the mRNA that codes for an amino acid carried by a tRNA. Transfer RNA also has a sequence of three nucleotides, an anticodon, whose base components pair with the codon found on the mRNA. When the tRNA binds to the mRNA codon at the ribosome, a specified amino acid is brought into the assembly line to be transferred to the growing polypeptide or protein. Completed proteins may be immediately functional or may, as is often the case in eukaryotic systems, require further post-translational modifications in the endoplasmic reticulum or Golgi apparatus. Modifications may include trimming of signal peptides, addition and trimming of sugars to form mature glycoproteins, or addition of phosphate groups.

Molecular Biology Tools

The introduction of recombinant DNA techniques has revolutionized biomedical research. Scientists now have the capability to identify and isolate a specific gene and study how it functions in normal and diseased states. Certain tools can be used to combine a gene of interest from one organism with genetic material from a different, rapidly dividing organism in order to produce large quantities of recombinant protein for clinical use. Selected tools used in recombinant DNA technology include restriction enzymes to "cut and paste" together DNA from different sources, vectors to transfer genetic material, and appropriate host cells to receive the recombinant construct (Lodish et al., 1995).

To facilitate manipulation of foreign DNA sequences, enzymatic tools must be used. Restriction endonucleases cut double-stranded DNA in precise locations, often leaving "sticky" ends that can be recombined with other DNA molecules. After cutting out a specified DNA sequence, the fragment generated may be pasted into a new location by first cutting the new site with a restriction enzyme and inserting the fragment. The final pasting of the fragment in place occurs through the action of an enzyme called *DNA ligase* that is capable of filling in the small gap left between the pasted molecule and the host DNA.

A vector is commonly used to transmit foreign genetic material into a host cell. Typical vectors used with many hosts include plasmids and bacteriophages. Plasmids are autonomously self-replicating, extrachromosomal, circular pieces of DNA. In clinical practice plasmids are best known for the role some play in transmission of antibiotic resistance among certain strains of pathogenic bacteria. With recombinant DNA technology, selected plasmids provide conveniently engineered transport systems for movement of foreign genes or DNA fragments into host cells. A bacteriophage or phage is a virus that infects a bacterial host. Phage can be used as carriers or vectors for introduction of a foreign gene into a bacterial host. Phage lambda is a common bacteriophage that infects *E. coli* and, via a lytic multiplication cycle, can generate hundreds of progeny phage within each infected bacterial cell. Both plasmid and phage vectors can be constructed so that infection of the host cell results in high levels of protein production from the foreign gene carried by the vector.

As previously mentioned, *E. coli* bacterial cells are commonly used as host cells for production of recombinant molecules. Other bacterial cells, yeast, and certain mammalian cells are also utilized. Although generation time and simplicity of genome favor bacterial and yeast host cells, some recombinant products must be expressed in mammalian cells in order to appropriately duplicate the desired protein. Post-translational modifications may be essential for full biologic activity of a protein and are typically accomplished only in eukaryotic systems. As a result, some products, for example recombinant erythropoietin, must be produced with cultured mammalian cells rather than bacterial hosts.

Production of Recombinant Products

A simplified sequence for production of a hypothetical recombinant product from gene X is shown in Figure 21–3 (Lodish et al., 1995). Although not detailed here, the process of identifying, isolating, and characterizing a given gene is demanding; these types of basic science efforts lay the groundwork for clinical application of recombinant gene products. Many recombinant drugs or reagents used in pharmaceutical processes are produced with bacterial cells as hosts and plasmids as vectors. The process of transferring a new gene to a bacterial host via a plasmid or phage vector is termed *transformation* or *transfection*, respectively. As shown in Figure 21–3, gene X is inserted or spliced into the gap in a plasmid cleaved by restriction endonucleases. DNA ligase seals the final connection between gene X and the plasmid.

Bacterial cells transformed with the recombinant plasmid are then screened to ensure presence of the plasmid. If the plasmid carrying gene X has been constructed to include antibiotic resistance genes, growth characteristics on antibiotic-impregnated agar plates may be used for selection of plasmid-containing bacteria. To ensure that plasmid-containing bacteria retained gene X, additional nucleic acid characterization techniques may be used that target specific gene X nucleotide sequences.

Nucleic acid characterization may be accomplished with several techniques. For example, samples of bacterial colonies growing on an agar plate may be transferred by overlaying the plate with a nitrocellulose filter. Portions of the bacterial colonies remain on the filter when it is removed. Further processing immobilizes DNA from each bacterium on the filter, including gene X if it is present. The filter is then processed and incubated with a probe that is chemically or radioactively labeled. The probe may represent the complete coding sequence of gene X (a complementary DNA [cDNA] probe) or may represent an 18 to 20 nucleotide fragment of gene X (an oligonucleotide probe). In either case, if the labeled probe forms complementary base pairs with sequences from gene X, it is said to hybridize to this sequence. Hybridization is specific and withstands washing of the filter to remove nonspecific probe binding. In the final step of the screening, labeled probe is detected with chemical processing or autoradiography. All bacterial colonies that contain gene X are marked by a signal generated by the hybridized, labeled probe. The same sequence of steps (transfer and immobilization of nucleic acid on a filter followed by hybridization with a labeled probe) may be employed to detect electrophoretically separated fragments of DNA or RNA (Fig. 21–4). These techniques are termed *Southern* or *Northern* blotting, respectively, and are important in the identification of nucleic acids in a variety of screening, cloning, and characterization procedures.

A final method that may be used for identification and amplification of specific nucleic acid sequences (in our example, gene X) utilizes the polymerase chain reaction (PCR) (Fig. 21–5). This technique is not necessarily used for screening bacterial clones but is often employed to more fully characterize cloned sequences. The PCR technique has also become an important diagnostic tool for detection of sequences associated with pathogenic organisms in clinical samples. As with in vivo DNA replication, PCR requires a DNA template to copy (in this case, gene X), sequence-specific primers to initiate the copying process, and deoxynucleotide triphosphates (dNTPs) to incorporate into the newly synthesized DNA.

First, double-stranded DNA from a few gene X-containing bacteria is denatured by heating to form single-

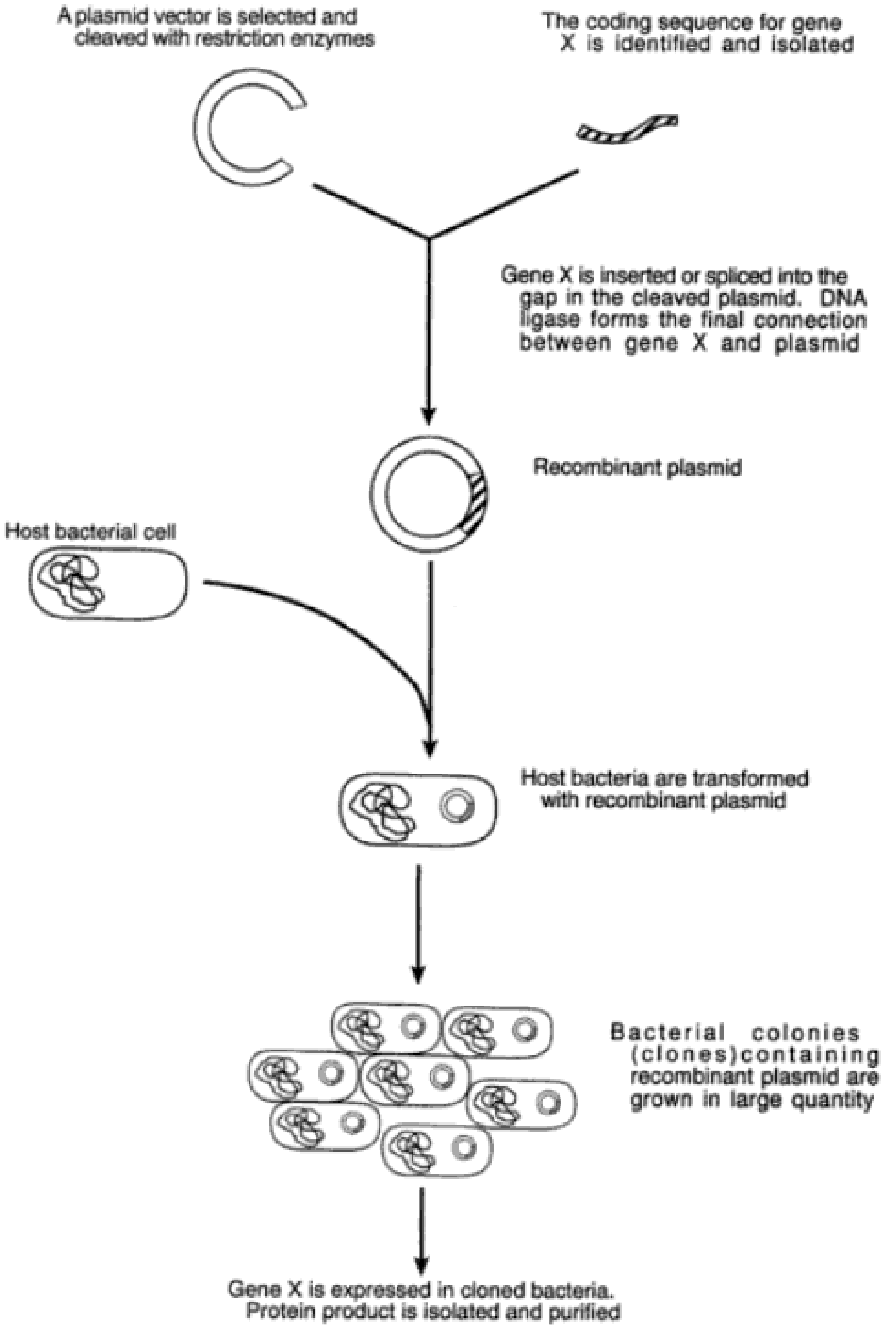
A plasmid vector is selected and cleaved with restriction enzymes
The coding sequence for gene X is identified and isolated
Gene X is inserted or spliced into the gap in the cleaved plasmid. DNA ligase forms the final connection between gene X and plasmid
Recombinant plasmid
Host bacterial cell
Host bacteria are transformed with recombinant plasmid
Bacterial colonies (clones) containing recombinant plasmid are grown in large quantity
Gene X is expressed in cloned bacteria. Protein product is isolated and purified

Figure 21–3. Outline of procedure for cloning a DNA fragment into a bacterial host using a plasmid vector.

stranded DNA template. Next, a pair of synthetic oligonucleotide primers is hybridized to the template DNA. Primers are short segments of DNA complementary to the regions on either side of the template DNA to be copied. Hybridization between the oligonucleotide primers and the single-stranded template DNA is facilitated by cooling of the reaction mixture. Finally, dNTPs and a heat-stable DNA polymerase (usually *Taq* polymerase) allow for extension of the primers along the length of the single-stranded DNA template yielding two complementary strands of DNA. At the end of one cycle the quantity of DNA is doubled, and the amount of template potentially available for the next cycle is also doubled. As the three steps are repeated, a chain reaction of DNA production results that exponentially expands the original template. For example, 20 cycles of amplification of one double-stranded DNA sequence results in a theoretical yield of approximately 1 million double-stranded copies. Amplified DNA sequences can be visualized on ethidium bromide-stained agarose gels or characterized in a variety of other ways, often including nucleic acid sequencing.

The final step in the production of our hypothetical recombinant product involves expression of the foreign gene (gene X in Fig. 21–3) in the host followed by purification of the recombinant protein. When the presence of the recombinant sequence has been verified, large populations of this clone are grown. In bacterial and yeast cells the expressed protein is often extracted from the whole organism. In some mammalian culture systems the foreign gene is engineered so that the expressed product is secreted from the cell and collected from the culture media. In either case, commercial production of recombinant products requires stringent quality control and extensive testing for purity and stability at each stage of the process. Physi-

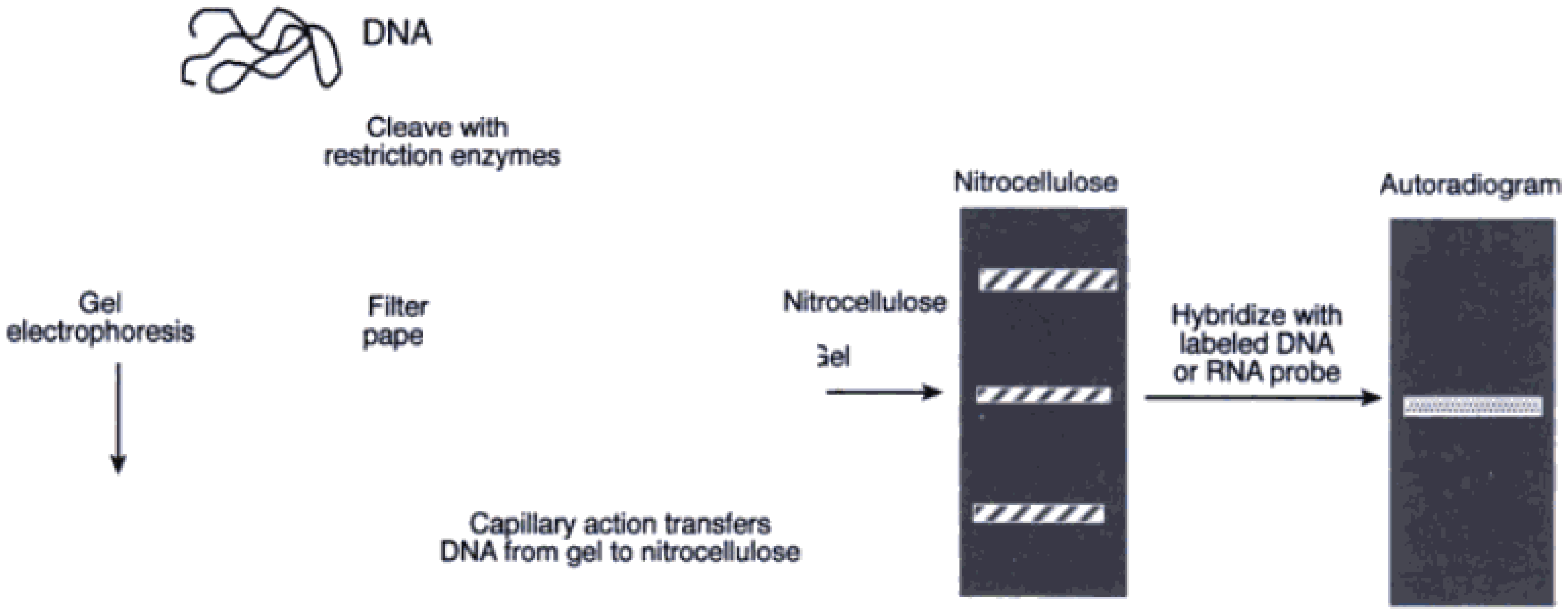
DNA
Cleave with restriction enzymes
Gel electrophoresis
Filter pape
Nitrocellulose
Gel
Nitrocellulose
Capillary action transfers DNA from gel to nitrocellulose
Hybridize with labeled DNA or RNA probe
Autoradiogram

Figure 21–4. Schematic depiction of procedure used for Southern blotting.

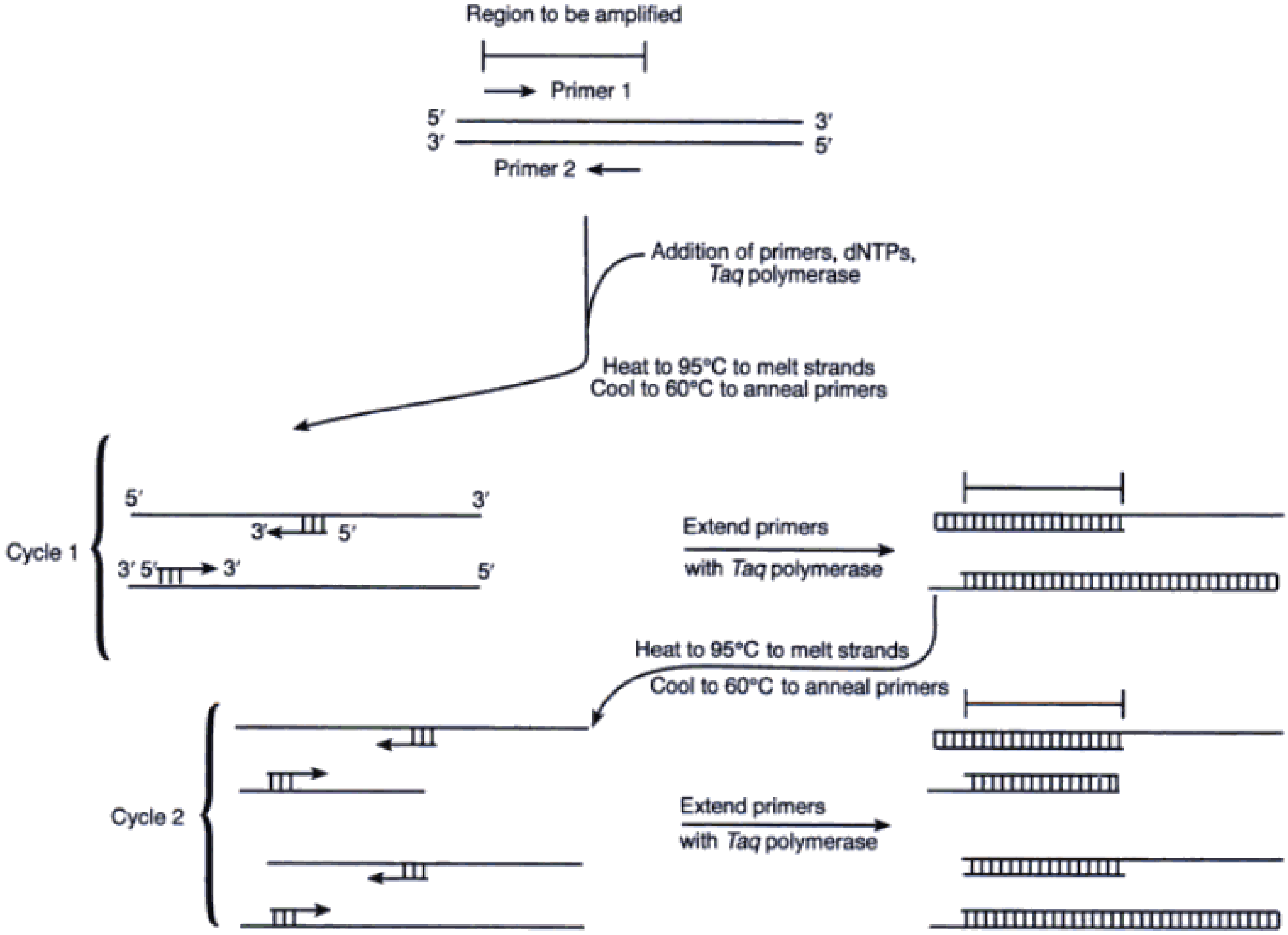
Region to be amplified
Primer 1
5′
3′
3′
5′
Primer 2
Addition of primers, dNTPs, Taq polymerase
Heat to 95°C to melt strands
Cool to 60°C to anneal primers
Cycle 1
5′
3′
3′
5′
3′ 5′
3′
5′
Extend primers with Taq polymerase
Heat to 95°C to melt strands
Cool to 60°C to anneal primers
Cycle 2
Extend primers with Taq polymerase

Figure 21–5. Polymerase chain reaction.

cal stability of a protein to unfolding, aggregation, and denaturation as well as chemical stability to oxidation, hydrolysis, racemization, and disulfide exchange are of concern with all protein products. Additional concerns with recombinant protein products include the ability of the genetically engineered culture system to resist mutation. Even point mutations in the genetic construct may result in a modified and biologically altered protein product.

RECOMBINANT PRODUCTS

Principles of Protein or Peptide Drug Therapy

Compared with conventional small drug molecules, proteins and peptides have several unique features and restrictions with regard to absorption, distribution, and routes of delivery. Successful therapeutic use of these agents depends on an understanding of their physicochemical and biologic characteristics, including molecular weight, biologic half-life, mechanism of degradation, and elimination and immunogenicity.

Absorption, Distribution, and Mechanisms of Degradation

Size, polarity, and charge hinder transport of many proteins and peptides, which can range in size from less than 600 to more than 100,000 daltons in their nonaggregated states. Protein and peptide permeation across intact biologic membranes such as gastrointestinal mucosa, ocular epithelium, and stratum corneum is very poor. Variable proteolytic decomposition in the gastrointestinal tract also contributes to slow and erratic oral absorption. Most pharmacokinetic data on protein drugs have been obtained after nonvascular parenteral administration. For the subcutaneous (SC), intramuscular (IM), and intraperitoneal (IP) routes, two mechanisms largely account for drug absorption (Rowland and Tozer, 1995). The first, diffusion through interstitial fluids and fenestrations in the linings of the vascular capillaries, is effective for small peptides (less than 5000 daltons). Larger polypeptides and proteins (greater than 20,000 daltons) rely on convective flow of interstitial fluids through lymphatic channels for absorption. Because lymph flow is slow, absorption from nonvascular parenteral sites continues for many hours. This offers the advantage of prolonged input for short half-life proteins. For example, glycosylated recombinant human granulocyte-macrophage colony-stimulating factor has a half-life of 68 minutes after intravenous (IV) administration but has a prolonged plasma concentration of 42 hours after SC administration (Hovgaard et al., 1992). Although prolonged absorption allows for less frequent administration of drug, release into the systemic circulation may be variable based on site of injection, temperature, and degree of rubbing at injection site.

Rapid degradation of peptides and proteins by peptidases and proteinases in the liver, blood, kidney, and subcutaneous tissues contributes to the short half-life of most peptide and protein drugs. As much as 20% of subcutaneously injected insulin has been found to be inactivated at the site of administration within 15 minutes (Reddy, 1992). Hepatic and renal clearance of many peptides also contributes to short half-life.

The relationship between drug and metabolite concentration as a function of time (pharmacokinetics) and the pharmacologic effects of a drug as a function of time (pharmacodynamics) are often more difficult to characterize for protein and peptide drugs than for small drug molecules. Because many peptide and protein drugs are very potent, detection and quantitation of low but relevant in vivo drug levels may be inadequate with existing analytical methods. In addition, assay methods for biologic activity of protein drugs may yield more qualitative than quantitative types of data, making standardization difficult.

Drug Delivery

The successful design of delivery systems for proteins and peptides depends on an understanding of the physicochemical and biologic characteristics mentioned earlier. Although the oral route of administration is often preferred for smaller drug molecules, this route is usually ineffective for most protein and peptide drugs unless drug modifications are made. Modifications may include formulation of drug with penetration enhancers and degradative enzyme inhibitors, bioreversible drug derivatization, and controlled or sustained-release delivery systems. Although a complete description of these modifications is beyond the scope of this discussion, some definitions and principles are noteworthy (Reddy, 1992).

Penetration enhancers are generally of four major types: chelating agents, bile salts, surfactants, and fatty acids. The latter three types enhance absorption by increasing the fluidity of the cell membrane barrier. In comparison, chelating agents, such as ethylenediaminetetraacetate (EDTA), precipitate divalent cations and form complexes with proteins; these complexes are thought to act on tight junctions between cells, thereby decreasing resistance to paracellular drug transport. Penetration enhancers are often formulated with enzyme inhibitors designed to prevent degradation of protein by peptidases and proteinases.

Bioreversible derivatization involves conversion of biologically active peptides to inactive pro-drugs. Many pro-drugs are derivatized to act as transient transport forms that protect amide and disulfide bonds in the peptide. A pro-drug is sufficiently labile to undergo eventual bioactivation via enzymatic hydrolysis, yielding the active drug. Hydrophobic derivatization has the added advantage of enhancing drug lipophilicity and absorption.

Carrier-mediated delivery and controlled or sustained-release delivery systems also offer advantages for delivery of protein or peptide drugs. One carrier-mediated system, liposome encapsulation, has been extensively studied. Liposomes are microscopic vesicles formed when desiccated phospholipids hydrate and form bilayers in the presence of a drug-containing aqueous phase. Liposome encapsulation has the advantage of enhancing drug absorption while slowing enzymatic drug degradation. Immunogenicity of the liposome itself and potential interaction with peptides and proteins are among the disadvantages of this system. Alternatively, controlled or sustained-release systems deliver drug at a predetermined rate for a definite period of time. Degradable and nondegradable polymer beads have been designed as vehicles to dispense proteins or peptides into the body in a physiologic manner over time. Effectiveness of these delivery systems is highly dependent on the protein to be dispensed.

Because the oral route of delivery presents various obstacles to protein and peptide drug absorption, alternative routes of administration have been explored. Some less conventional routes include nasal, buccal, pulmonary, transdermal, ocular, rectal, and vaginal. Protein drugs administered by these routes potentially encounter fewer proteolytic enzymes and for a shorter time period. In addition, limited dilution of drug maintains a favorable concentration gradient for absorption. Although all of these routes show promise with selected drugs, it is not possible to accurately predict which route will be optimal for a given drug without extensive testing. The profile for drug absorption will also vary between species. In general, protein stability and movement of large proteins through or around membrane barriers still present the greatest obstacles. Examples of innovative approaches around these problems include transdermal delivery by iontophoresis in which a constant, low-level electric current is used to push drug through existing pathways in the skin such as hair follicles and sweat glands (Davis, 1992). A related method, electroporation, uses ultrashort pulses to induce changes in underlying skin that allow drug passage. An enzyme-responsive transdermal delivery system for insulin administration has been proposed in which an insulin reservoir device generates an electric pulse to open skin pores, takes a blood sample, processes it using a glucose-oxidizing enzyme, and accordingly adjusts the release and delivery of an appropriate amount of insulin to the body. The financial incentives to design improved delivery systems for protein and peptide drugs has increased with the need to effectively utilize potent recombinant products in humans.

Immunogenicity

A final therapeutic concern associated with administration of recombinant proteins and peptides is the body's potential immune response to these products. Factors that contribute to immunogenicity of proteins within homologous systems (e.g., human recombinant products administered to humans) include aggregation, denaturation, presence of N-terminal methionine, incorrect or lack of appropriate post-translational modifications, and amino acid substitutions or deletions. Maintaining fidelity of genetic constructs and protein products is important in limiting development of host antibodies to recombinant proteins. Successful use of recombinant human or murine products in different species (i.e., heterologous systems) depends on conserved homology of amino acid sequences between the two species. If sequence homology is poor, the product may be inhibited or blocked completely from binding to appropriate receptor populations in the target species. Homology differences may also lead to an initial therapeutic effect followed by antibody formation and loss of efficacy, anaphylactic reaction, or cross-reactivity against the native protein in the patient. Recombinant human erythropoietin (rhEPO) and recombinant human granulocyte colony-stimulating factor (rhG-CSF) both eventually elicit therapy-limiting antibody production in small animal patients (Cowgill, 1992; Lothrop et al., 1988).

Table 21–1 lists selected recombinant products currently available or in clinical trials for use in human or veterinary medicine. As is evident, most recombinant products available or soon to be available are designed for use in humans. Recombinant human (rh) products already in use in small animals include rhEPO, insulin (rhIn), interferon-α2A (rhIFα2A), and rhG-CSF. In addition, experimental and clinical veterinary studies have been conducted using tumor necrosis factor (rhTNF), interleukin 2 (rhIL-2), interleukin 3 (rhIL-3), and granulocyte-macrophage colony-stimulating factor (rhGM-CSF). Recombinant canine and bovine G-CSF and GM-CSF are being used experimentally but are not commercially available Extensive studies have also been conducted into the safety and efficacy of recombinant bST, which was approved for use in the United States in 1994. Although only a few recombinant vaccines are currently on the market, this is a major area for introduction of recombinant products in the near future.

Hematopoietic Growth Factors

Recombinant Human Erythropoietin

Erythropoietin (epoetin alfa; Epogen) (Giger, 1992; Adamson and Eschbach, 1990; Cowgill, 1991, 1992) is a glycoprotein that stimulates red blood cell production. It is produced in the kidney and stimulates the division and differentiation of committed erythroid progenitors in the bone marrow. The correct generic name for rhEPO is epoetin alfa. Endogenous production of erythropoietin is normally regulated by the level of tissue oxygenation. Hypoxia and anemia generally increase the production of EPO, which in turn stimulates erythropoiesis. In patients with chronic renal failure, production of EPO is impaired and EPO deficiency is a primary cause of anemia. Recombinant human EPO contains 165 amino acids and has a molecular weight of 30.4 kD. It has the same primary structure as human urinary EPO, and its clinical efficacy has been well documented in human clinical trials. The erythropoietic effects are dose dependent and stimulate a rapid reticulocytosis and sustained increase in hematocrit value, red blood cell count, and hemoglobin concentration. Significant improvement in quality of life and clinical well being are seen with resolution of anemia (Adamson and Eschbach, 1990).

The ability of rhEPO to stimulate erythropoiesis in mice, rats, primates, dogs, and cats has been documented under experimental conditions. In both dogs and cats, rhEPO promotes initial reticulocytosis and a rapid progressive increase in hematocrit value, red blood cell count, and hemoglobin concentration within 2 to 3 weeks of initiation of therapy (Fig. 21–6A) (Giger, 1992). Recombinant human EPO has no consistent effects on leukocytes or platelets in dogs but transiently increases platelet counts in individual dogs. Cats show significantly increased platelet counts during the initial phases of treatment (Cowgill, 1991). Most treated animals show improvement in quality of life in terms of appetite, weight gain, alertness, and increased energy.

Table 21–1. Selected Recombinant Products

Generic Name	Trade Name	Indication	Species	Status
Immune modulators				
Interferon-α2A	Roferon-A	Cancer therapy, antiviral	Human	Approved
Interferon-α2B	Intron A	Cancer therapy, antiviral	Human	Approved
Interferon-αN3	Alferon N	Antiviral	Human	Approved
Interferon-γ1B	Actimmune	Immunotherapy	Human	Approved
Interferon-β	Betaseron	Immunotherapy	Human	Approved
Interleukin-2	Proleukin	Immunotherapy, cancer therapy	Human	Approved
Interleukin-3		Immunotherapy, cancer therapy	Human	Clinical trial
Interleukin-1α and -1β		Enhance vaccine response	Bovine	Experimental
Tumor necrosis factor		Cancer therapy	Human	Clinical trial
Hematopoietic growth factor				
Granulocyte colony-stimulating factor	Neupogen	Myelosuppression Immunostimulant	Human	Approved
Granulocyte-macrophage colony-stimulating factor	Leukine	Myelosuppression Immunostimulant	Human, canine bovine	Approved
Erythropoietin	Epogen	Anemia of chronic renal disease	Human	Approved
Tissue repair				
Epidermal growth factor		Corneal repair	Human	Clinical trial
Platelet-derived growth factor		Wound healing	Human	Clinical trial
Transforming growth factor-β antagonist		Wound healing	Human	Experimental
Hormone therapy				
Insulin	Humulin	Diabetes	Human	Approved
Growth hormone	Protropin	Hypopituitary dwarfism	Human	Approved
	Posilac	Enhanced milk production	Bovine	Approved
Atrial peptide	Auriculin	Congestive heart failure	Human	Clinical trial
Other				
Tissue plasminogen activator	Activase	Acute myocardial infarction	Human	Approved
Superoxide dismutase		Acute myocardial infarction	Human	Clinical trial
DNAse	Pulmozyme	Cystic fibrosis (mucolytic) Chronic bronchitis	Human	Approved

Adverse effects that may be associated with rhEPO therapy include refractory anemia or erythroid hypoplasia. Progressive nonresponsive decreases in hematocrit value, red cell count, and hemoglobin concentration may occur in as many as 50% of treated animals after several (usually >4) weeks of therapy (Fig. 21–6B) (Adamson and Eschbach, 1990). Failed erythropoiesis is associated with the appearance of anti-rhEPO antibodies. Recovery from the antibody-induced anemia depends on the magnitude of the antibody titer, its rate of disappearance, and the animal's endogenous ability to secrete erythropoietin. Support via blood transfusions may be necessary to return the patient to pretreatment hematologic status. Other side effects may include polycythemia, vomiting, seizures, injection discomfort, skin reactions, and systemic hypertension (Cowgill, 1992).

Pet owners should be counseled about the benefits and risks of rhEPO therapy and provide informed consent before its administration. Treatment should be reserved for animals with overt signs of anemia and significantly decreased hematocrit levels. In both dogs and cats, an initial dosage of 100 U/kg SC three times weekly will promote

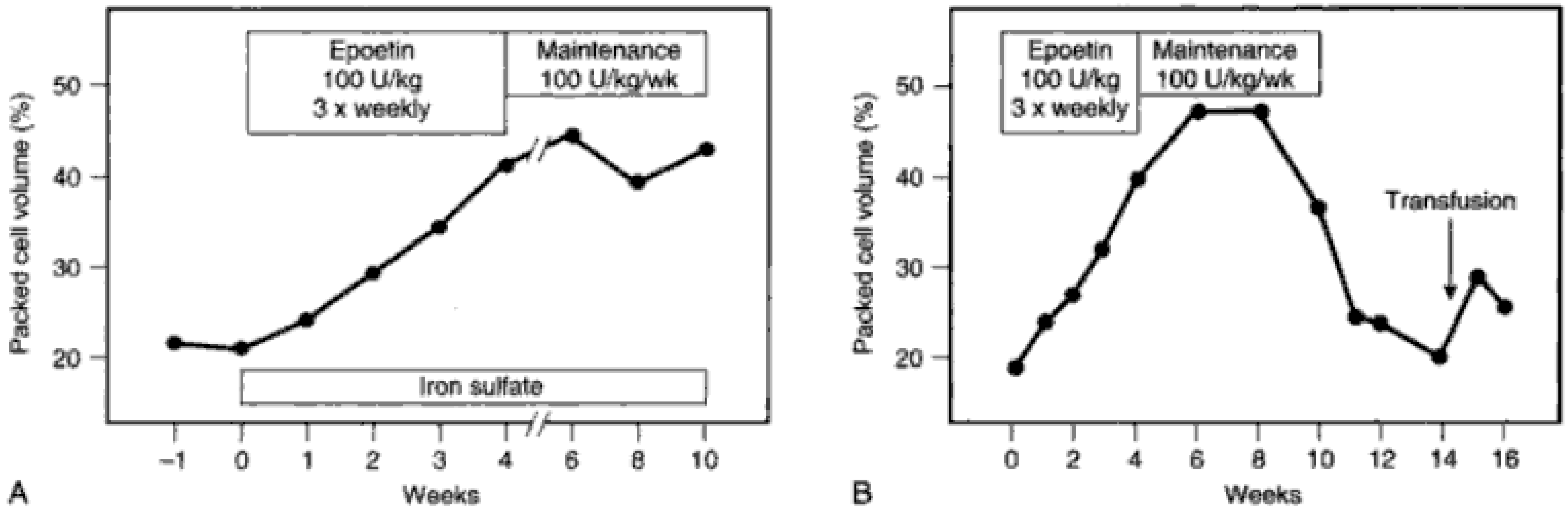

Figure 21–6. Response of anemic dogs with chronic renal failure to epoetin alfa. *A*, Typical rapid increase in packed cell volume. *B*, Development of nonregenerative anemia as a result of antierythropoietin antibodies. (From Giger U: Erythropoietin and its clinical use. Compend Contin Educ Pract Vet 1992; 14: 25.)

an effective response. This dosage is maintained until a target hematocrit value is attained (35% to 45% in dogs, 30% to 40% for cats). When the lower end of the target hematocrit value is reached, dosage interval may be decreased to twice weekly and eventually once weekly. Weekly dosage of rhEPO may also be adjusted down during maintenance therapy. Supplementation with iron sulfate will foster the therapeutic response if iron availability is suboptimal. Weekly or biweekly assessments of hematocrit value and clinical response should be made until the hematocrit value stabilizes.

Recombinant human EPO is produced by mammalian cells transformed with the human EPO gene. The protein is secreted from commercial-sized cultures of cells, purified from growth media, and formulated into the final product. No species-specific recombinant erythropoietin products are available.

Recombinant Human and Recombinant Canine Granulocyte Colony-Stimulating Factor

G-CSF is one of several hematopoietic factors that stimulate proliferation and maturation of myeloid precursors in bone marrow. G-CSF specifically stimulates neutrophil precursors and enhances antibody-dependent cytotoxicity, superoxide production, and Fc receptor expression. Limited stimulation of monocytes also occurs (Mishu et al., 1992). Clinical trials in humans have shown that rhG-CSF reduces morbidity and mortality associated with myelosuppression and neutropenia secondary to chemotherapy or bone marrow transplantation, cyclic neutropenia, congenital agranulocytosis, and infectious diseases such as HIV (Lieschke and Burgess, 1992). Studies in cattle have explored the effectiveness of recombinant human and bovine G-CSF and GM-CSF in dealing with infectious disease processes when enhanced neutrophil response is desirable (Kehrli et al., 1991).

Recombinant human G-CSF (Neupogen) administered to normal dogs at a dosage of 5 µg/kg twice daily caused significantly increased neutrophil counts as early as 12 hours that persisted for 2 to 3 weeks with continued rhG-CSF administration. Therapy was limited by development of antibodies that caused the neutrophil count to drop precipitously on about day 23 of treatment (Lothrop et al., 1988). Similar observations were made in cats treated with the rh product (Fulton et al., 1991). In both dogs and cats, neutralizing antibodies limited prolonged therapy with rhG-CSF. Recombinant human G-CSF continues to be used clinically in veterinary medicine for short-term therapy of neutropenia associated with chemotherapy or with acute infectious disease.

Recombinant canine G-CSF as been found to be safe and effective in both dogs and cats (Obradovich et al., 1991, 1993; Mishu et al., 1992), and therapy is not limited by development of neutralizing antibodies. A dose-dependent increase in neutrophil and monocyte counts occurs when rcG-CSF is given SC at a typical dosage of 5 µg/kg per day. Obradovich et al. (1991) reported initial, dramatic increases in mean neutrophil counts in dogs (greater than 30,000/µL) that occurred within 24 hours of the first dosage. This was followed by a 5-day period of moderate increase or plateau with a subsequent rise to peak at 19 days (mean neutrophil counts greater than 70,000/µL). Discontinuation of rcG-CSF administration resulted in rapid decline in neutrophil numbers to a normal range within 5 to 6 days. Although dosage rates and mean cell counts have varied between studies, all investigators agree that a dose-dependent increase in neutrophil and monocyte counts occurs without adverse effects as long as rcG-CSF is administered. Figure 21–7 illustrates a typical, dose-dependent, subtly biphasic response of normal dogs to two courses of rcG-CSF (Mishu et al., 1992). The same study and others have demonstrated the effectiveness of granulocyte stimulation in cyclic neutropenia, autologous bone marrow transplantation, and during cancer chemotherapy. Both the duration and severity of neutropenia induced by chemotherapy were decreased.

Recombinant Human and Recombinant Canine Granulocyte-Macrophage Colony-Stimulating Factor

GM-CSF stimulates production of granulocytes, macrophages, and eosinophils and acts together with IL-3 and EPO to stimulate erythroid precursors and thrombogenesis (Ogilvie, 1993). GM-CSF enhances cell-killing functions of neutrophils, including oxidative metabolism, phagocytosis, lysozyme secretion, antibody-dependent cellular cytotoxicity and tumoricidal cytotoxicity. Recombinant human GM-CSF (Leukine) has limited effectiveness in dogs as a result of neutralizing antibody production and possibly as a result of limited sequence homology between the human and canine factors. Recombinant canine GM-CSF at a dose of 30 µg/kg per day, however, has been shown to increase

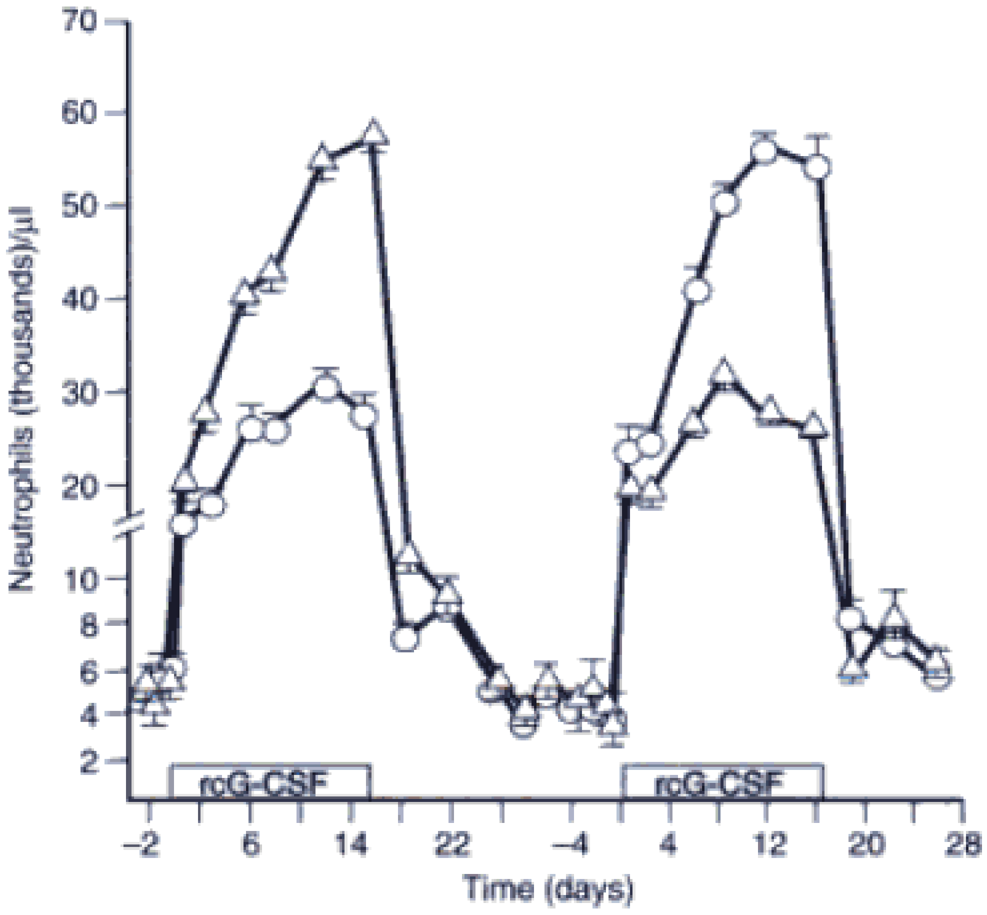

Figure 21–7. Segmented neutrophil count of clinically normal dogs that were given two courses of recombinant canine granulocyte colony-stimulating factor (rcG-CSF) 60 days apart. △ = 5 µg/kg, q12h, first treatment; and 1 µg/kg, q12h, second treatment. ○ = 1 µg/kg, q12h, first treatment; and 5 µg/kg, q12h, second treatment. (From Mishu L, Callahan G, Allebban Z, et al: Effects of recombinant canine granulocyte colony-stimulating factor on white blood cell production in clinically normal and neutropenic dogs. J Am Vet Med Assoc 1992; 200: 1957.)

granulocyte counts (MacEwen, 1995). Because GM-CSF simulates several cell types, good therapeutic potential exists for its use in the treatment of a variety of diseases associated with neutropenia and anemia. Unfortunately, neither recombinant canine G-CSF nor GM-CSF is currently commercially available.

Other Hematopoietic Growth Factors

Stem cell factor (SCF), also referred to as mast cell growth factor and ligand for *c-kit* (an oncogene-encoded receptor), serves as an early hematopoietic growth stimulus. Consistent with findings in other species, recombinant canine SCF (rcSCF) has less effect on neutrophil counts in dogs than rcG-CSF or rhGM-CSF (Dale et al., 1995). When administered alone, rcSCF treatment was only effective in high doses and was often accompanied by adverse side effects, including acute muzzle edema and chronic dermal induration with basophil accumulation. Treatment of cyclic neutropenia with rcSCF (20 to 50 μg/kg per day) and rcG-CSF (0.5 to 1 μg/kg per day) increased mean neutrophil counts synergistically, suggesting that combination protocols may be of some value in selected cases (Dale et al., 1995).

Macrophage colony-stimulating factor (M-CSF) has been shown to increase circulating monocytes and promonocytes in humans. The human product does not appear to be active in dogs (MacEwen, 1995).

Hormone Therapy

Recombinant Human Insulin

Insulin is composed of 51 amino acids arranged in two polypeptide chains, designated A and B, which are linked together by two disulfide bridges. Insulin is synthesized and secreted by the β-cells of the pancreas via two inactive precursors, preproinsulin and proinsulin, which are sequentially cleaved to form the active hormone (Chance, 1981). Insulin therapy is essential for treatment of type I or insulin-dependent diabetes mellitus (IDDM), which is the most common form of the disease in dogs and 50% to 70% of cats.

Commonly available commercial insulin preparations are categorized by onset, duration, and intensity of action. Regular crystalline insulin has a very rapid and short-lived effect compared with intermediate-acting preparations such as NPH (isophane) or Lente Insulin. Protamine zinc insulin (PZI) and Ultralente Insulin are considered long acting. Mixtures of short- and long-acting insulins have been developed to more closely approximate the physiologic effects of endogenous postprandial insulin release. In all cases, the therapeutic effects of insulin administration will vary somewhat between individuals (Chance, 1981).

Various preparations are available for each type of insulin to be used. Until the early 1980s, all insulin was prepared by extraction of bovine or porcine pancreatic tissue with subsequent hormone purification. The increasing incidence and diagnostic detection of diabetes worldwide, coupled with changing trends in food animal markets, stimulated pharmaceutical companies to seek alternative sources of insulin independent of animal glands. By the mid-1980s, recombinant human insulin (rhIn; Humulin) began to be produced by a process involving the enzymatic conversion of the biosynthetic precursor of insulin, human proinsulin. The human gene for proinsulin is inserted into *E. coli* bacteria and grown in a fermentation process. The fermentation step is stopped by heat sterilization to eliminate any possibility of contamination by *E. coli* organisms. The connecting or C peptide is then enzymatically cleaved from the human proinsulin to produce human insulin. Recombinant insulin has been extensively studied in human patients new to insulin therapy and in patients transferred from animal-source insulin. Studies have confirmed the efficacy, safety and favorable pharmacokinetic and immunogenic profile of rhIn in people (Chance, 1981).

Although all types of commercial insulin may be administered to dogs and cats, the immunogenicity of insulin products may vary as a result of species-related differences in insulin homology. Canine, human, and porcine insulin have a high degree of homology, while feline insulin is more closely related to the bovine hormone (Hallden, 1986). It has been suggested that an initial, mild anti-insulin response may prolong the duration of action by interfering with insulin degradation (Bolli, 1984). Hence, some recommend initial utilization of beef/pork insulin for the dog and cat in order to elicit a mild antibody response against the beef (in dogs) or pork (in cats) component. If problems with insulin resistance develop, however, selection of the most homologous product is recommended for each species (recombinant human product for dog and purified bovine insulin for cats) (Nelson, 1995). Availability of beef and beef/pork insulin preparations has become more limited in the past few years. Both PZI and beef/pork Ultralente Insulin have been discontinued by Lilly. Human recombinant Ultralente (Humulin-U, Lilly) and purified beef Ultralente (Squibb-Novo) remain available.

Growth Hormone

Growth hormone (GH; somatotropin, Norditropin) is secreted by somatotropes in the anterior pituitary gland and acts, at least in part, by stimulating hepatic generation of insulin-like growth factor-1 (IGF-1) (Matthews, 1991). Growth hormone is secreted in response to declining blood glucose levels and is suppressed when blood glucose is high. Clinical disorders of growth hormone secretion or function may result in dwarfism (GH deficiency) or acromegaly (GH excess).

In dogs, growth hormone deficiency can occur as a primary endocrine abnormality resulting in pituitary dwarfism or as an acquired deficiency leading to GH-dependent dermatosis. In either case, therapy involves GH replacement. Recombinant human somatotropin (Humatrope) and recombinant bovine somatotropin (bST; Posilac), as well as a therapeutically equivalent drug, recombinant human met-growth hormone (rh-metGH, Protropin), are available. Both human and bovine GH are biologically active in the dog and may be administered at a dose of 0.1 IU/kg SC three times weekly for 4 to 6 weeks. Epiphyseal plate closure may limit alterations in body stature in response to GH administration. Dermatologic responses may be seen within 4 to 6 weeks in the form of visible hair growth. Adverse effects of GH therapy in dogs may include transient or permanent diabetes mellitus secondary to elevated somatotropin levels and development of neutralizing antibodies to heterologous GH (Wilkens et al., 1996). In all cases, animals with GH deficiencies should be thoroughly evaluated for other endocrine imbalances and treated accordingly. The effects of recombinant canine somatotropin on the metabolic and histologic aspects of bone healing have recently been investigated in dogs (van Herpen et al., 1994). With an unstable ostectomy gap model, recombinant canine GH was shown to enhance bone healing and to offer a potential for treatment of fractures in metabolically compromised or geriatric patients.

Although a discussion of bST is beyond the scope of this chapter, it is worth noting that this is the mostly widely used recombinant veterinary product. This product has been approved for several years in some countries and in the United States since 1994. A large amount of data has been collected regarding the optimal use of bST in a variety of husbandry conditions. Studies conducted by the National Institutes of Health, the state of Wisconsin, the American Medical Association, the Endocrine Society, and the American Council on Science and Health have all concluded that milk and meat from bST-treated cattle are safe for human consumption. A number of reviews of bST are available (Juskevich and Guyer, 1990; NIH Technology Assessment Conference, 1991).

Immune Modulators

Molecular biologic tools have greatly enhanced our ability to identify and begin to understand the function of multiple factors involved in immune responsiveness. Recombinant preparations of potent immune modulators have been investigated in cancer therapy and in the treatment of infectious disease. As indicated in Table 21–1, a number of recombinant immune modulators are available for use in human medicine. A handful of these have been investigated and are being used in veterinary medicine. Despite the promise, relatively few recombinant immune modulators have had a significant impact on veterinary therapeutics.

Recombinant Human Interferon-α2A

Interferons are a family of glycoproteins produced by leukocytes and macrophages (interferon-α [IFN-α]) fibroblasts and parenchymal cells (IFN-β), and antigenically or mitogenically stimulated lymphocytes (IFN-γ). These three families of glycoproteins are known to cause diverse antiviral, antitumor, and immunomodulatory effects. Although the effects of IFN-γ and IFN-β tend to be more species specific, recombinant human IFN-α2A (Roferon-A) has been found to be effective across species lines and has seen the widest use (Moore, 1996). Feline interferon (rfIFN) has been produced in silkworms infected with recombinant baculovirus encoding a feline interferon cDNA. Recombinant fIFN from this system is a mixture of alpha, omega, and beta types and has been shown to have similar pharmacokinetic properties to human interferons and to have antiviral properties (Ueda et al., 1993).

Interferon-α has been used most extensively and in a variety of applications in veterinary medicine. The responsiveness of domestic animal cell lines to different rhIFN preparations showed the following order of decreasing sensitivity to rhIFN-α: bovine, ovine, porcine, feline, equine, and canine (Bridgman et al., 1988). Besides species sensitivity, additional considerations in the therapeutic use of IFN-α include selection of recombinant product over natural IFN preparations, high versus low dosage regimen, and route of administration.

Natural interferons generally consist of a mixture of multiple interferon subtypes that differ slightly in composition and biologic activity. Recombinant products must rely on the biologic activity of a single molecular IFN type and therefore may demonstrate less inherent activity in a given species. As a result, recombinant IFNs, which must be used at a somewhat higher comparative dose, may be more likely to induce a neutralizing host anti-IFN antibody response with chronic use (Moore, 1996).

Multiple studies have shown that high doses of interferon may cause adverse effects, including hyperthermia, anorexia, and malaise; these effects may be related to a self-destructive host inflammatory response or to immunosuppression. High doses also exacerbate the problem of anti-IFN antibody production and appear to promote IFN resistance. In comparison, low doses (0.1 to 4.0 IU/kg) of IFN-α have proved beneficial in the treatment of acute and chronic viral infections in humans and animals (Stanton et al., 1987; Georgiades, 1993).

The side effects associated with high-dose IFN treatment are more likely to appear when IFN is parenterally administered. Alternatively, oral interferon administration, although seemingly an unlikely route for absorption of protein, has been shown to be effective by altering oropharyngeal-associated lymphoid tissue. Orally administered interferon is thought to trigger release of soluble cytokines, such as interleukin-1, from oropharyngeal macrophages and lymphocytes. These cytokines in turn modulate systemic immune function by recruitment and stimulation of lymphocytes that cause a significant amplification of IFN's biologic effect. Hence, IFN acts less as a typical circulating therapeutic agent and more as an external trigger for endogenous biologic responses (Weigent et al., 1984; Bocci, 1991).

Treatment of several viral diseases of the cat, including feline leukemia virus (FeLV), feline immunodeficiency virus, and feline infectious peritonitis, has been augmented with interferon with varying success. Oral rhIFN-α is commonly administered at a dose of 30 U per cat per day for 1 week; maintenance therapy may include alternate-week interferon treatment. Experimental and clinical studies have reported that low doses of rhIFN-α prevent disease development in cats experimentally infected with FeLV (Tompkins, 1988; Weiss, 1991). Combination therapy using zidovudine (3′-azido-3′-deoxythymidine) and rhIFN-α to treat established FeLV infection resulted in a significant reduction in circulating virus during a 49-day treatment period. The antiviral effect of this treatment was limited by production of neutralizing antibodies to IFN. Additional studies suggested that a combination of rhIFN-α, zidovudine, and adoptive lymphocyte transfer served to reconstitute antiviral humoral immunity, counteract immunosuppression, and induce reversal of retroviremia in four of nine cats receiving combined therapy (Zeidner et al., 1993). A retrospective study of feline ocular disease attributed to herpesvirus showed no clear advantage to inclusion of oral IFN in treatment protocols; however, the number of cats receiving oral IFN was low (n = 3), and treatment protocols varied (Stiles, 1995).

Although in vitro sensitivity of canine cells to rhIFN-α is low, anecdotal reports suggest that rhIFN-α is effective in the treatment of selected viral diseases, including parvoviral enteritis (Kolokoltsox et al., 1993).

Recombinant Human Tumor Necrosis Factor-α and Recombinant Human Interleukin-2

Cytokines are a diverse group of proteins produced by a number of cell types (Paul and Seder, 1994). These proteins are critical in the regulation of immune responses and in the differentiation of various T-cell subsets. Several cytokines have been cloned from a variety of species; recombinant products developed for clinical use in humans are listed in Table 21–1. Recombinant hIL-2 and rhTNF have been investigated for use in veterinary medicine.

Interleukin-2 is produced by antigen-stimulated or mitogen-stimulated T cells. Interleukin-2 functions are not considered species specific and include stimulation of CD4+ and CD8+ cell growth, partial regulation of B-cell development, and stimulation of lymphokine activated killer cells. Interleukin-2 is a member of the hematopoietin family and is therefore similar in structure to IL-4 and GM-CSF (David, 1995; Helfand et al., 1992).

Tumor necrosis factor-α is one of the most abundant substances produced by macrophages and is also secreted by activated T cells, natural killer cells, and mast cells (David, 1995). Interferon-γ endotoxin, and migration inhibitory factor stimulate TNF production. Tumor necrosis factor mediates responsiveness to lipopolysaccharide and therefore plays a primary role in host defense against gram-negative bacteria. Responses to low-dose lipopolysaccharide include enhanced macrophage function, activation of B cells, and fever. Tumor necrosis factor participates in the protective inflammatory response by inducing expression of adhesion molecules and cytokines and by activating or enhancing the function of neutrophils, macrophages, and eosinophils. It is cytotoxic to tumor cells in vitro and causes hemorrhagic necrosis of tumors in vivo. The effects of TNF are considered to be largely species nonspecific (Helfand et al., 1992).

Recombinant human IL-2 has been shown to increase tumor-directed cytotoxic activity of canine peripheral blood mononuclear cells in vitro (Jardine et al., 1989) even at low, clinically relevant dosages (Helfand et al., 1994). These studies led to examination of IL-2, alone and in combination with other cytokines, as an immunotherapeutic agent in tumor-bearing dogs. Sequential administration of rhTNF and rhIL-2 to dogs with cancer revealed synergistic immunologic and antitumor effects (Jeglum et al., 1990; Moore et al., 1991). A maximally tolerated dose of rhTNF of 125 mg/m^2 for 3 days followed by 1.5×10^6 U/m^2 rhIL-2 SC for 9 days was determined (Moore et al., 1991). Limited or no toxicity was reported for rhIL-2, whereas common toxicities associated with TNF administration included fever, nausea and vomiting, weakness and malaise, and, infrequently, mast cell degranulation (Jeglum et al., 1990). Thus far, mast cell tumors and oral mucosal melanoma are the only canine tumors found to be responsive to IL-2/TNF therapy (Jeglum et al., 1990; Moore et al., 1991).

Vaccine Technology

Because principles of immunology are critical to an adequate understanding of vaccinology, this topic is often considered in immunology rather than pharmacology texts. Although an in-depth discussion of immunology fundamentals is beyond the scope of this text, consideration of the contribution of recombinant technology to the science of vaccinology is important.

A vaccine is a collection of immunostimulatory determinants delivered to antigen-presenting macrophages, antibody-secreting B cells, and helper, effector, and cytotoxic T cells. For optimal effect, vaccines should induce immediate effector responses in addition to induction of anamnestic protection on future exposures (Hilleman, 1994). Ideal vaccines are safe, effective, and practical regardless of the technology utilized to produce them. Safety depends on purity and freedom from adventitious agents or chemical contaminants, low or no probability for transmission of live agents to secondary hosts, lack of integration or recombination of vaccine elements with host cells, lack of oncogenic qualities, availability of reliable procedures for quality control, and acceptably low environmental impact. Efficacy is reflected in patient protection with lasting humoral and cellular immunity, genetic stability of vaccine in composition and expression, and predictable and reproducible clinical responses. Practical issues that should be considered in vaccine development include ease of administration, number of doses needed for effectiveness, polyvalency, ability to distinguish vaccinated animals from recovered carriers, stability during storage and transport (e.g., heat lability), and reasonable cost-to-benefit ratio (Hilleman, 1994).

Vaccines are traditionally categorized as nonreplicating, inactivated (killed), or attenuated live. Recombinant technology is now important in the production of selected vaccines in both of these categories (Yilma, 1994). In the inactivated vaccine category, recombinant technology has facilitated production of specific viral proteins to make subunit vaccines. The first recombinant vaccine was developed and approved for use in humans in 1984 based on a genetically engineered hepatitis B surface protein as the immunizing antigen (McAleer et al., 1984). An important veterinary vaccine against FeLV (Genetivac) was similarly developed by expression of the cloned gene for major envelope glycoprotein, gp70 FeLV subgroup A, in *E. coli* (Marciani et al., 1991). A recombinant subunit vaccine to envelope glycoprotein of feline immunodeficiency virus was developed but has not proved effective (Tozzini et al., 1995). Advantages of recombinant antigen production for vaccines include purity of final preparation and high concentration of selected, presumably optimally antigenic, determinants. Compared with nonrecombinant killed virus alternatives, recombinant vaccines may contain 10-fold to 1000-fold more potentially reactive protein. A disadvantage associated with recombinant subunit vaccines, however, relates to the poor immunogenicity of small, pure protein preparations (Yilma, 1994). A key feature of the efficacy of recombinant subunit vaccines therefore lies in the proper selection and inclusion of immunostimulatory, adjuvant substances. Adjuvant substances may include detergents (e.g., a saponin derivative is used in Genetivac), peptides, cloned cytokines, and a number of other proprietary substances.

Compared with inactivated (killed) products, attenuated live virus vaccines offer enhanced immunogenicity related to increased antigenic stimulation as a result of viral replication within the host (Hilleman, 1994). This advantage may be offset in some cases by the greater lability of live virus products, necessitating refrigeration, and by the possibility of disease induction in debilitated animals. Reversion of attenuated viral strains to virulence, or mutation to new strains in the patient or arthropod vector, may also be of concern. Many methods of viral disablement have been utilized for vaccine production. Attenuation may be accomplished naturally by adaptation of live viruses to different species (e.g., use of a vaccinia virus, cowpox, to immunize humans against smallpox) or by chemical or genetic means. Genetic engineering in the form of site-directed mutagenesis has been used effectively to inactivate viruses for vaccine production (Hilleman, 1994).

Besides application of recombinant technology in the production of traditional inactivated and attenuated live vaccine products, a new generation of recombinant live agent, vectored vaccines, is on the horizon (Yilma, 1994). Recombinant live agent, vectored vaccines are produced by the insertion and expression of heterologous genes for immunologically relevant substances in a variety of vectors. The immunizing antigen is therefore produced in the context of a replicating, nonpathogenic vector without the threat of disease induction. Expression vectors have been derived from virus, bacteria, yeast, and animal cells; viral vectors that have been utilized experimentally include papilloma, adeno, herpes, retro, pox, and baculovirus (a virus that infects insect cells) (Yilma, 1994). Although many products are under development, and a few have been approved for commercial use, experience with recombinant vectored vaccines has made it clear that factors eliciting protective responses are more complicated than first believed. In particular, mode of presentation of antigen within host tissues appears to be of equal importance with selection of immunizing antigen construct (Zarlenga, 1994).

A complete explanation of all expression systems is beyond the scope of this discussion; however, one system, vaccinia virus (VV), serves as a good example to highlight some of the advantages potentially offered by recombinant vaccines. Vaccinia virus has a wide host range, allowing viral replication and foreign gene expression in a number of hosts. Lyophilized VV is heat stable, can be reconstituted easily, and can be administered by several routes. The large genome of VV allows for a number of insertion sites for foreign sequences. This in turn raises the possibility of multiple gene insertions resulting in a polyvalent vaccine capable of immunizing simultaneously against many disease agents (Moss, 1991).

The strategy for using VV as a vector involves first constructing a plasmid carrying a chimeric gene with three important elements. The first element is a VV promoter; promoters are regulatory sequences positioned upstream of (also referred to as 5′ to) the gene of interest. Transcription factors bind to sequences in the promoter region to regulate expression of the second important element of the plasmid, the foreign gene, located downstream to the promoter. Finally, the promoter/gene construct is flanked on either side by DNA from a nonessential region of the VV genome. The genetically engineered plasmid is then introduced into tissue culture cells infected with wild-type (wt) VV. The chimeric plasmid gene is incorporated into the wt VV genome by homologous recombination made possible by the VV flanking regions in the plasmid construct. Recombinant viruses are identified and isolated from wt viruses in a variety of ways, depending on the details of the recombinant construct (Yilma, 1994).

The strategy described has been used to develop a number of experimental products, including a promising vaccine against rinderpest (Yilma et al., 1988) and an approved rabies vaccine (Brochier et al., 1995). A recombinant VV expressing the glycoprotein of rabies virus (VVTGgRAB) has been developed and used for oral immunization of wildlife. Five campaigns of fox vaccination using oral baits took place between 1989 and 1991 in Belgium (Brochier et al., 1995). These efforts produced a drastic decrease in the incidence of rabies and the elimination of the disease from 80% of the initially infected area. Follow-up studies of these efforts assessed the risk of recombination between engineered vaccine virus and other orthopox viruses in the target fox population. Although these studies were not comprehensive, findings indicate that the risk of recombination between vectors and endemic viruses in foxes was low (Crouch et al., 1995).

Although many recombinant vaccines show great promise, the ability of a specific preparation to stimulate a protective immune response depends on immunogenicity of the expressed protein and production of neutralizing antibodies. As previously noted, highly successful vaccines may depend on innovative combinations of genetic constructs with other immunostimulatory agents. Both IFN-γ and IL-2 genes have been inserted into live agent recombinant vaccines to further attenuate the virus and to enhance immune stimulation (Yilma, 1994). These and other efforts are essential to the ultimate success of many products now under development.

An increasingly promising area of recombinant vaccine development is referred to as DNA immunization. In this method, intramuscular or subcutaneous injection of naked plasmid DNA containing a gene of interest was found to result in direct in vivo gene transfer (Krishnan et al., 1995). A biolistic DNA gene gun that propels plasmid DNA into the skin has been used in many of these studies. Although a low number of cells at the injection site internalize the DNA, expression of the plasmid is often persistent over several months or longer. In the case of gene gun delivery to the dermis, expression of plasmid in Langerhans cells is thought to play an important role in successful antigen presentation (Webster et al., 1994). In the systems studied, expression of heterologous genes was typically not a result of chromosomal integration of the plasmid DNA but resulted from autonomous expression of plasmid sequences (Krishnan et al., 1995).

DNA immunization has potential advantages because expression of antigens in their native forms improves processing and presentation to the immune system. Efforts have been made to enhance immunogenicity of expressed antigens by inclusion of short immunostimulatory DNA sequences within plasmid constructs (Sato et al., 1996). An additional advantage of DNA vaccines is prolonged expression of antigen at injection sites that may decrease the total number of vaccine doses needed for protection. As with recombinant vectored systems, potential polyvalency of DNA products and ease of vaccine administration are desirable. Although no veterinary DNA vaccines are yet available, many influenza studies with constructs ultimately designed for human use have been accomplished with the ferret as an animal model (Donnelly, 1995).

Advances in immunization have not been limited to antiviral products. Major efforts have been made to utilize recombinant technology to produce effective parasite and bacterial vaccines as well (Zarlenga, 1994). Production of a recombinant antigen vaccine against infection in sheep with the parasite *Taenia ovis* was the first effective, inactivated product against a parasitic infection in animals or humans (Lightowlers and Rickard, 1993). Initiatives to develop vaccines against arthropods have resulted from an increased problem with insecticide resistance and with public outcry against potential chemical contamination caused by insecticides. Although a number of products are under development and diverse strategies are being employed to add more, only a few vaccines have been shown to be efficacious. Perhaps the best example at present is a vaccine based on a recombinant antigen derived from the cattle tick, *Boophilus microplus*, carrier of a number of cattle fevers (Kay and Kemp, 1994). Experimental vaccination of dogs with a recombinant gene product derived from the tick-borne spirochete *Borrelia burgdorferi* has been used to impede Lyme disease (Chang et al., 1995). Oral administration of recombinant allergens derived from arthropods, such as flea or house dust mite, have been used experimentally to try and induce tolerance to sensitizing antigens in dogs (Deplazes et al., 1995).

Monoclonal Antibodies

Monoclonal antibodies (MAbs) have been extensively investigated for the treatment of cancer. As early as 1895, investigators injected cancer cells into animals to develop antiserum for treating sarcoma patients. Later, Paul Ehrlich proposed that "receptors" were secreted by cells of the immune system in response to foreign antigens. These receptors, or antibodies, were believed to target proteins, that is, antigens, associated with malignant cells (Himmelweit, 1957). Immortalization of antibody-producing spleen cells by fusion with mouse myeloma cells was accomplished in classic experiments by Kohler and Milstein (1975) that represented a major technologic breakthrough in MAb production.

Effective, murine antibody-based cancer therapies have been complicated by production of patient anti-idiotypic antibodies that neutralize the murine MAb and cause its rapid clearance from the circulation. The science of MAb production has advanced from the hybridoma technology of Kohler and Milstein (1975) to the production of "humanized" therapeutic antibodies designed to escape host antiantibody defenses. Recombinant technology has been used to engineer complete antibodies containing therapeutically desirable constant and variable regions.

Production of MAbs has been accomplished in a variety of ways, but high-level antibody expression remains a challenge to expanded application of MAb in therapeutics. Recombinant antibodies have been produced in various eukaryotic systems, including production in the milk of transgenic mice and goats (Bebbington, 1995). Large-scale production of MAbs has been accomplished in dairy animals by microinjection of fertilized eggs with a DNA construct in which the genes encoding heavy and light chains of the antibody are linked to a milk-specific promoter. Transgenic females resulting from this process are capable of producing recombinant antibody in their milk. Since the successful cloning of a sheep from a mature sheep cell by Wilmut et al. (1997), the potential for production of antibodies and other recombinant pharmaceuticals in cloned, transgenic animals has increased. Use of cloned, transgenic animals in pharmaceutical production enhances the biochemical homogeneity of material from different animals by eliminating variability in background genetic factors.

Approximately 80 MAb-based products are in development for diagnosis, imaging, and therapy in human medicine. Antibodies have been tagged with radioisotopes, toxins, and drugs in efforts to develop effective "magic bullets" for cancer therapy and other applications. In veterinary medicine, a MAb (MAb231) has been developed that targets canine lymphoma cells and has been reported to mediate antibody-dependent cellular cytoxicity (Rosales et al., 1988). The median survival time for dogs treated with chemotherapy alone was shorter than for dogs treated with chemotherapy plus MAb231 (Jeglum, 1992).

Despite the fact that MAbs have filled the biotechnology pipeline, relatively few human or veterinary products are recognized, as yet, as unqualified therapeutic successes in the fight against cancer.

FUTURE DIRECTIONS IN GENE THERAPY

The simplest definition of gene therapy is based on the idea that certain diseases caused by monogenic defects can be treated and potentially cured by insertion and expression of a normal copy of the dysfunctional or missing gene. Hence, diseases such as adenosine deaminase deficiency caused by a change or deletion in a single enzyme were the first targets for gene therapy. Based on currently approved protocols, the framework for gene therapy has become much broader. The distinction between recombinant DNA therapeutics and gene therapy is increasingly difficult to make (Roth and Cristiano, 1997).

In human and veterinary medicine, gene therapeutics is most often used to treat cancer. Strategies include ex vivo and in vivo cytokine and tumor antigen gene transfer, drug sensitization with genes for pro-drug delivery, and use of drug-resistance genes for bone marrow protection in high-dose chemotherapy. In the context of cancer treatment, gene therapy is rarely used alone and is most often tried as a supplement to existing therapies. For example, transduction of bone marrow cells with a drug-resistance gene has been investigated as a means of sparing marrow cells during chemotherapy (Sorrentino et al., 1992). Although this type of therapy does not replace a defective or missing gene product, the gene and product provided have therapeutic value.

Augmentation of the immune response against cancer has been attempted with recombinant DNA constructs expressing cytokines and lymphokines. Protocols may be based on expression of gene constructs in tumor-infiltrating lymphocytes, tumor cells, or fibroblasts that can be genetically engineered and then administered, usually autologously, to the patient. Cytokine genes utilized include IL-2, IL-4, IL-7, IL-12, GM-CSF, and TNF (Roth and Cristiano, 1997). Various vaccines expressing tumor-specific antigens, for example, gp100 melanoma antigen, or co-stimulatory molecules to enhance tumor antigen presentation are also being investigated (Rosenberg, 1995).

Tumor cells can also be transduced with a gene whose product can convert a relatively nontoxic pro-drug administered systemically to a toxic metabolite. An early protocol with this strategy transfected brain cells with a retroviral vector expressing the herpes simplex virus thymidine kinase (HSV-TK) gene. Systemic ganciclovir that entered the tumor cell was then metabolized to cytotoxic ganciclovir triphosphates by cells expressing HSV-TK (Culver et al., 1992).

Our understanding of the role of dominant oncogenes and tumor suppressor genes in the etiology of cancer has increased steadily over the last two decades. Normal homologues of oncogenes, termed *protooncogenes*, are essential for signal transduction, transcription, and a number of other key cellular functions. Point mutations, amplifications, translocations, and rearrangements can, however, convert protooncogenes into activated dominant oncogenes capable of contributing to cellular transformation. Tumor suppressor genes often regulate gene transcription and cell proliferation and, when dysfunctional or deleted, have a permissive effect on transformation of cells (Bishop, 1991).

Gene therapy targeted against dominant oncogenes attempts to nullify the effect of expression of an activated oncogene product. Methods that have been used to accomplish this include antisense blockade of mRNA translation, antisense oligonucleotide-enhanced degradation of oncogene-encoding mRNA, ribozymes that cleave oncogene mRNA, and intracellular single chain antibodies (Roth and Cristiano, 1997). Antisense technology involves introduction into a cell of a gene construct that has a base sequence complementary to the RNA sequence targeted for inhibition. As an example, antisense inhibition of a member of the ras oncogene family, K-ras, has been shown to reduce the growth rate of human lung cancers in vitro and in vivo in mice (Georges et al., 1993; Mukhopadhyay et al., 1991).

Replacement of inactivated or absent tumor suppressor genes into a transformed cell could theoretically restore normal regulation of cell proliferation. For example, introduction of an important tumor suppressor gene product, p53, into cells with mutant or deleted p53 is sufficient to cause arrest of unregulated cell proliferation (Cai et al., 1993). p53 delivered by adenovirus vector constructs has been shown to inhibit growth of rat gliomas, human head and neck cancers, and human colon cancers in mice and can mediate p53 gene expression in bladder and liver cancer (Roth and Cristiano, 1997). An encouraging aspect of some oncogene therapy is the observation that transduced cells can mediate bystander killing of nontransduced cells, thus enhancing the antitumor effect of gene therapy (Takahashi et al., 1992).

As with development of effective recombinant vaccines, one of the most important areas of research into gene transfer is in vector design. The viral vectors mentioned earlier in the context of vaccine development, including retro, adeno, adeno-associated, herpes, pox, vaccinia, and baculovirus, are also important to the advancement of anticancer gene therapy. Nonviral vectors including liposomes and naked DNA hold promise for gene therapy as well.

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Control of Pain in Small Animals: Opioid Agonists and Antagonists and Other Locally and Centrally Acting Analgesics

22

Dawn Merton Boothe

INTRODUCTION: DEFINITION OF PAIN AND ITS RECOGNITION
Classification of Pain
Transmission of Pain
Response to Pain and Stress
CONTROL OF PAIN
Levels of Consciousness
Endogenous and Exogenous Pain Control
OPIATES
Definitions
Mechanism of Action
Pharmacokinetics
Adverse Effects
  Central Nervous System
  Gastrointestinal Tract
  Other Effects
Drug Interactions
POWERFUL PURE AGONISTS
Morphine
Fentanyl
Sufentanil
Oxymorphone
Meperidine
MILD TO MODERATE PURE AGONISTS
Codeine
Miscellaneous Drugs
MIXED AGONISTS AND ANTAGONISTS
Butorphanol
Buprenorphine
Pentazocine
Nalbuphine
NARCOTIC ANTAGONISTS
Naloxone
Nalorphine
Nalbuphine
Naltrexone
THERAPEUTIC USE OF OPIOID ANALGESICS
OTHER CENTRALLY ACTING DRUGS
Tranquilizers and Sedatives
α_2-Agonists
ANTICONVULSANTS AND BEHAVIOR-MODIFYING DRUGS
LOCAL ANESTHETICS
SPECIAL CONSIDERATIONS FOR CONTROL OF PAIN IN ANIMALS
Geriatric Patients
Surgical Pain
Critically Ill Patients
Cranial Trauma
Epidural Analgesia

INTRODUCTION: DEFINITION OF PAIN AND ITS RECOGNITION

Classification of Pain

Aside from the moral issues, the successful control of pain can impact therapeutic success. Physiologic pain can be considered as a protective mechanism, leading the animal to withdraw from a potentially damaging stimulus. Pain can, however, become the source of injury itself (pathologic pain). If pain is too severe for the animal to accommodate, a state of distress can develop (Hansen and Hardie, 1993). Beyond protection, pain rarely has any useful function and is associated with dramatic and potentially life-threatening physiologic changes (Cousins, 1986; Anthony, 1995; Potthoff, 1989). Physiologic responses to distress include gastrointestinal lesions, immunosuppression, and hypertension. In human patients, failure of response to treatment, hospitalization duration, and hospitalization costs can be positively correlated with failure of effective pain control. The sensation of pain can be associated with a marked adrenergic (catecholamine) release, which may cause life-threatening hypertension or cardiac arrhythmias. In addition to acute physiologic responses to pain, the persistence of pain can stimulate changes at the level of the nociceptor and central nervous system (see Transmission of Pain).

Pain can be classified in several ways, including source (physiologic, which is protective, versus pathologic, which reflects damage), location (neuropathic, resulting from neurologic damage; nociceptive, resulting from tissue damage; visceral, associated with abdominal or thoracic pain; or somatic originating from musculoskeletal damage, both of the latter divided into superficial or deep), duration (acute, which is abrupt in onset and resolves in 24 to 72 hours, versus chronic, which persists for several weeks), and severity (mild, moderate, and severe). Acute pain results from traumatic, surgical, or infectious events. It is abrupt in onset, relatively short in duration, and is generally alleviated by analgesics. In contrast, chronic pain is a long-standing physical disorder or emotional distress that is usually slow in onset and long in duration. Examples include degenerative joint disease and some cancer pains. The transmission of chronic pain is not well described, and knowledge regarding neural pathways is limited. Chronic pain is seldom alleviated by analgesics and frequently responds to tranquilizers combined with environmental manipulation and behavioral conditioning.

Transmission of Pain

Nociception is the neural response to the application of a noxious stimulus. The nociceptive system is the most effective system for eliciting an arousal response of any of the sensory systems. The nociceptive response is comprised of a nociceptor and three neuron chains originating in the peripheral tissues and ending in the cerebral cortex. Nociceptors are free nerve endings that respond to noxious stimuli (Fig. 22–1) located in blood vessels, pleura and peritoneum, many visceral organs, skin, periosteum, subchondral bone, joint capsule, muscle, and tendons. The nociceptor projects as neuron 1 into the spinal cord, ascends as neuron 2 to the reticular formation of the brain, and then as neuron 3 to the cerebral cortex.

Stimulation in the reticular formation results in emotional reaction to pain (anxiety, depression, suffering), whereas stimulation in the cerebral cortex leads to conscious perception and interpretation of pain. The first-order neuron can also synapse with another neuron to cause a local reflex that can be myoneural or sympathetic in action (e.g., release of norepinephrine, smooth muscle spasm, vasoconstriction). The nociceptive reflex can occur without perception of the painful stimulus that initiated the reflex. Pain perception is indicated by voluntary actions. Chemical mediators are important components of the nociceptor reflex and offer a target of pharmacologic modulation. Mediators of pain and/or stress include adrenocorticotropic hormone; glucocorticoids; vasopressin, oxytocin, brain opioids, catecholamines, angiotensin II; endorphins/enkephalins; vasoactive intestinal peptides, substance P (centrally); and eicosanoids (prostaglandins, leukotrienes), tissue kininogens (bradykinin), histamine, serotonin, potassium, proteolytic enzymes, and others (peripherally) (see Chapter 16).

The transmission of pain is carried by Aδ, C, or Aβ fibers. Aδ fibers are fast and are responsible for pain that is sharp and acute. They transmit somatic and parietal pain. Because the receptors are discrete, animals can localize the pain. C fibers are slow and transmit dull, aching, burning, or throbbing pain that is difficult to localize. Aβ fibers are slower than C fibers and transmit stimuli associated with vibration, stinging, or tickling.

The perception of pain can be enhanced by two phenomena: hyperalgesia and central sensitization. The phenomenon of hyperalgesia reflects the response of nociceptors to a stimuli in a more vigorous manner at a lower threshold than central sensitization. Primary hyperalgesia occurs in response to the presence of inflammatory mediators at the nociceptor, whereas secondary hyperalgesia reflects response in surrounding tissues, probably due to sensitization of surrounding nociceptors (Cross, 1994; Paddleford, 1999). Central sensitization follows exposure of the spinal cord to a large number of nociceptive impulses resulting in hypersensitization. As a result, stimuli that might otherwise be considered innocuous cause a perception of pain. The phenomenon of central sensitization precludes an "as needed" approach to the treatment of pain with opioids. It may be because of this phenomenon that efficacy of the opioids in controlling pain is enhanced if given before the generation of pain.

Response to Pain and Stress

One of the more difficult aspects of acceptable control of pain for the clinician is detection or recognition of pain

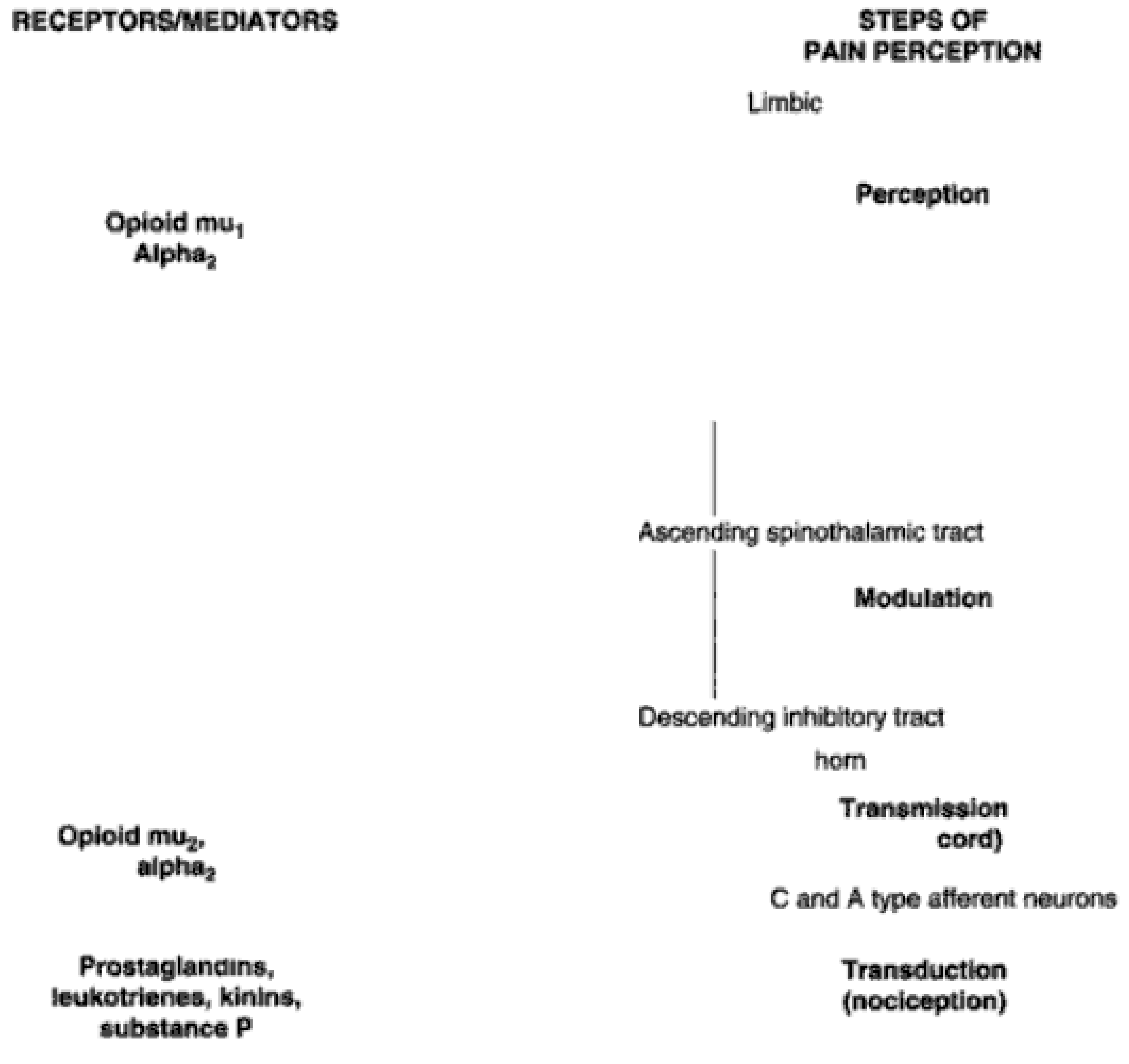

Figure 22–1. Pain pathways and relevant receptors. The steps of pain (on right) are mediated by different signals or receptors (on left).

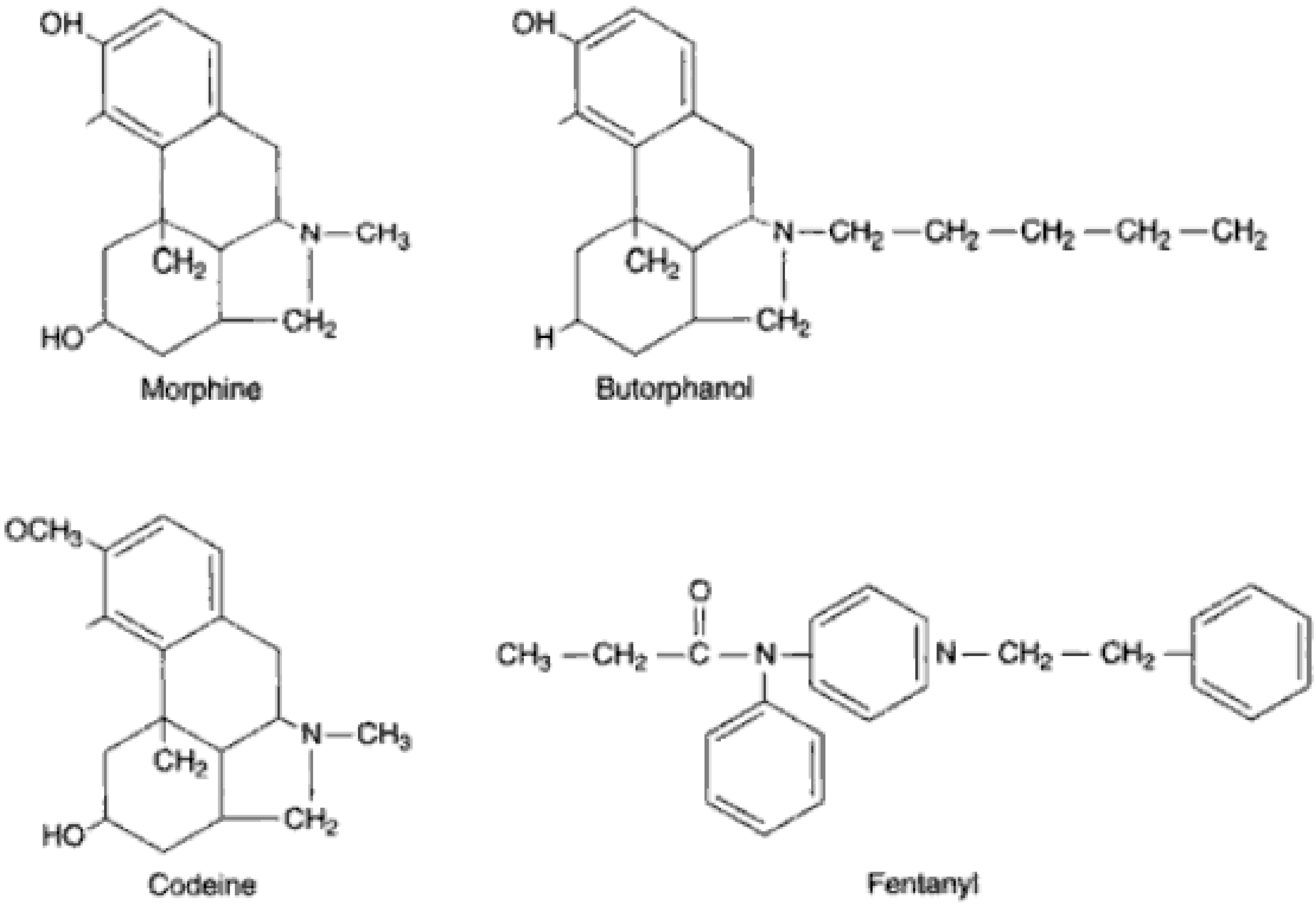

Figure 22–3. Structures of selected opioids.

tive interactions between drugs and these receptors provide no analgesia. Rather, many of the adverse effects of the opioids are mediated at these receptors, including dysphoria, hallucinations, respiratory stimulation, and some of the vasomotor responses to opioids. *Delta* receptors, as well as smooth muscle and lymphocytes are located in the CNS; other sites are likely to be discovered. Interaction with delta receptors appears to modulate, among other effects, emotional behavior and immunomodulation (see Chapter 19).

The likelihood of each of these effects to occur after an opioid interaction with the receptor depends on the type of interaction that occurs between the chemical and the receptor. It is likely that species differences in receptor number, location, and specificity or sensitivity to the various drugs are important to differences in response to the opiates. Drug companies have attempted to "improve" the effects of opioids, that is, to enhance the desired pharmacologic effect while minimizing undesirable effects, by chemically altering the natural opioids. Semisynthetic drugs are made from simple chemical changes of morphine (codeine) or thebaine (e.g., oxycodone, etorphine, and naloxone). Other morphine derivatives include apomorphine (an emetic), hydrocodone, and oxymorphone (Reisine and Pasternak, 1996). Improvements have altered the state of the interaction between the opioid and the receptor. Opioids can interact with these receptors as *agonists* (bind and stimulate) or *antagonists* (block and inhibit the effect). *Mixed agonists* exhibit variable binding specificities at each receptor type, with some sites being agonistic and other sites antagonistic. *Partial agonists* do the same as mixed agonists, but their positive interaction with the receptors occurs with less than full activity at some of the receptors. Thus, many of the varied effects of these drugs (particularly synthetics) result from agonistic actions at one receptor and antagonist activities at another.

Table 22–1. Receptor Selectivity for Clinically Useful Opioids

Drug	Mu	Delta	Kappa
Buprenorphine	P	—	Ant
Butorphanol	P	—	Ag
Codeine			
Fentanyl	Ag		
Morphine	Ag		Ag
Nalorphine	Ant		Ag
Nalbuphine	Ant		Ag
Naloxone	Ant	Ant	Ant
Naltrexone	Ant	Ant	Ant
Pentazocine	P		Ag
Sufentanil	Ag	Ag	Ag

Ag = agonist; Ant = antagonist; P = partial agonist.

The primary pharmacologic effects of all opioids are analgesia, euphoria, and sedation (without loss of consciousness) (Reisine and Pasternak, 1996). The magnitude of each effect varies among species. The cellular mechanism and the pharmacologic effects of the opioids probably reflect several different effector mechanisms, including altered calcium flux, decreased cyclic adenosine monophosphate (increased cyclic guanosine monophosphate), inhibition of neurotransmitter release (acetylcholine, glutamic acid, dopamine, seratonin, substance P [particularly peripherally], norepinephrine), or modulation of a potassium channel. Control of pain occurs without diminution of other senses. The degree of analgesia depends not only upon the receptor stimulated but also upon the location of the receptor. Interaction with central mu receptors might provide greater analgesia than interaction with spinal mu receptors. Administration of morphine at both spinal and supraspinal sites results in synergistic analgesic effects, with a 10-fold reduction in the total dose of morphine necessary at either site alone (Reisine and Pasternak, 1996).

the dose increases. Rate, tidal volume, and minute volume all decrease. Respiratory depression is, however, rarely a clinical concern except in cases of overdose, or in the presence of pulmonary dysfunction in cases of standard doses (Reisine and Pasternak, 1996). Opioids should be used cautiously in patients with compromised respiratory function. Patients may appear to be handling the drugs well but in fact may be utilizing compensatory mechanisms, such as increased respiratory rates (Reisine and Pasternak, 1996). Concentrations of CO_2 may be increased, and respiratory centers may already be less sensitive to CO_2. The administration of an opioid may be dangerous in such situations.

Opioids have precipitated attacks of asthma in human anesthetized patients, probably due to histamine release. The importance of this in animals is not clear. In the developing fetus, use of opioids in the pregnant animal can lead to marked respiratory depression with little to no effect on the mother because of the underdeveloped blood-brain barrier in the fetus (Reisine and Pasternak, 1996).

Cardiac depression (particularly bradycardia) is caused by some drugs; pretreatment with atropine can reduce the incidence. The risk of hypotension is increased with drugs that also cause histamine release, such as morphine (but not oxymorphone) (Robinson et al., 1988). Histamine antagonists (H_1) partially block morphine-induced hypotension; naloxone completely blocks it in human patients (Reisine and Pasternak, 1996; Muldoon et al., 1983). Fentanyl and its congeners are less likely to cause hypotension associated with surgery in part because they do not cause histamine release (Reisine and Pasternak, 1996). Volume replacement should be instituted before administration of morphine derivatives causing histamine release in patients that are hypovolemic. Central nervous system depression tends to preclude the use of opioids in syndromes such as shock, severe cranial trauma, and diseases associated with respiratory compromise.

Opioids increase intracranial pressure due to increased concentrations of CO_2 and cerebral vasodilation. Cerebral spinal fluid pressure also increases (Reisine and Pasternak, 1996). These effects may be exaggerated after head injury. The effects on intraocular pressure are not clear and may vary with the species. In humans, accommodation is increased with a decrease in intraocular pressure. Opioids cause miosis in humans, and mydriasis occurs in some species.

Convulsions occur in some species when opioids are administered in high doses. Mechanisms probably include inhibition of γ-aminobutyric acid and may be more likely with morphine-like drugs (Reisine and Pasternak, 1996). The convulsant effects of some opioids can be reversed by naloxone (Reisine and Pasternak, 1996), suggesting that drugs with antagonistic actions (e.g., butorphanol, buprenorphine) at some receptors might be preferred in the seizuring patient. The impact of opioids on epileptic patients is not clear.

Sedation is common with opioid use, depending on the drug and the species (i.e., in the dog due to mu or less so, kappa receptor stimulation) and can be a disadvantage or an advantage, depending on the clinical situation. In cats, opioids can cause dysphoria and psychomotor activity (due to sigma receptor stimulation). Some of these effects might be avoided by administration of tranquilizers.

Morphine and related opioids depress the cough center. Respiratory depression and cough suppression do not appear to be related. Thus, antitussive opioids need not necessarily cause respiratory depression (Reisine and Pasternak, 1996).

In contrast to depression, opioids directly stimulate the chemoreceptor triggering zone and thus may cause nausea and vomiting. Individual differences in the emetic response to opioids are marked in humans, but the amount of variability is not clear in animals (Reisine and Pasternak, 1996). In patients in whom opioids cause emesis, after subsequent administration, opioids act as antiemetics, blocking further response by the chemoreceptor triggering zone to opioids. Actions at the vestibular apparatus may also be responsible for emesis. The emetic effects that typify administration of opioids as sole agents do not typically occur in the postoperative, sick, or pain-ridden patient. Butorphanol has been used in some species as an antiemetic to control vomiting induced by cisplatin (Schurig et al., 1982).

Tolerance, physical dependence, and withdrawal occur, but should not be considered an adverse reactions to opioid use. Despite the lack of correlation between tolerance and physical dependence with incidence of drug abuse, concern about these two physiologic responses has led to a reluctance of physicians to use these drugs to their fullest capacity to control pain in human patients. Tolerance occurs if higher doses are required to produce the same (analgesic) effect, whereas physical dependence requires continued administration in order to avoid clinical signs characteristic of withdrawal.

Both tolerance and physical dependence reflect adaptation of the target cells. Changes in nitric oxide or neurotransmitters or their pathways have been implicated as contributors to the development of tolerance (Reisine and Pasternak, 1996). Tolerance will most likely develop for analgesia, euphoria, sedation, respiratory depression, nausea or vomiting, and suppression of cough. Physical dependence occurs as exogenous opioids replace endogenous opiates. Opioids affect numerous physiologic systems that became inbalanced before drug administration. A new balance or equilibrium is established in the presence of the drug (O'Brien, 1996), and abrupt discontinuation of the drug requires rapid readjustment to a new equilibrium, predisposing the patient to withdrawal. Withdrawal is generally manifested as signs opposite to the original effects caused by the drug and reflects CNS hyperarousal as readaptation occurs to the absence of the drug (O'Brien, 1996). Pharmacokinetic variables may be important to the development of withdrawal (O'Brien, 1996).

The advent of tolerance and physical dependence has lead to scheduling or classification of many members of the opioid class of analgesics as potential substances of abuse. The actual class designated for some of the less "risky" drugs varies among the states. Pure agonists tend to be scheduled in Class II or III; mixed or partial agonists tend to be scheduled in Class IV or V, depending on the abuse potential. Butorphanol has recently been rescheduled from Class V to Class IV. It is not clear how long drug administration must occur before tolerance, physical dependence, and withdrawal are of clinical concern. Morphine dependence has been described in dogs (Martin et al., 1976). In dogs, however, mixed agonists/antagonists or partial agonists are associated with the least risk of dependence; among the opioids studied, buprenorphine appears to be the least likely to cause dependence (Jacob et al., 1979). Opioids can be discontinued in drug-dependent human patients without causing signs typical of withdrawal by decreasing the dose 25% to 50% every couple of days. In human patients suffering from withdrawal, clonidine, an α_2-adrenergic agonist, minimizes the autonomic symptoms of opioid withdrawal (O'Brien, 1996).

Gastrointestinal Tract

In addition to effects at the chemoreceptor triggering zone, opioids have direct effects in the gastrointestinal tract. Hydrochloric acid secretion is generally decreased but occasionally may be increased (Reisine and Pasternak, 1996). Tone of smooth muscle in the antral portion of the stomach and upper duodenum will increase, despite decreased gastric peristaltic motility. Passage of endoscopic or other equipment through the stomach can be precluded for up to 12 hours after administration. Drug or food movement through the stomach likewise can be delayed (Reisine and Pasternak, 1996). In the small intestine, and particularly in the upper small intestine, resting tone (segmental) is increased, and propulsive activity is markedly decreased (Reisine and Pasternak, 1996). Initial stimulation of gastrointestinal motility may result in defecation; subsequent depressed gastric motility may cause constipation with prolonged use.

Opioids also decrease small intestinal secretions, while water absorption increases. In the presence of secretory diarrheas, morphine-like opioids inhibit movement of electrolytes and water into the lumen, probably through inhibition of the stimulatory effects of prostaglandin E_2, acetylcholine, or vasoactive intestinal peptide (Reisine and Pasternak, 1996). Because of increased transit time allowing more complete absorption of luminal contents, opioids may be contraindicated in patients suffering from obstructive gastrointestinal diseases and those associated with bacteria or toxin production. Opioids also decrease biliary and pancreatic secretions (Reisine and Pasternak, 1996). Morphine-like opioids, however, cause contraction of the sphincter of Oddi and increased bile duct pressure (Reisine and Pasternak, 1996; Vieira et al., 1993; Roebel et al., 1979).

Other Effects

Ureteral tone may increase and the voiding reflex of the bladder may be diminished due to increased tone of the external sphincter and increased volume of the urinary bladder. Morphine appears to have antidiuretic effects (Reisine and Pasternak, 1996). Inhibitory effects on uterine tone may prolong labor; hyperactivity induced by oxytocin can be normalized with morphine. Neonatal health may be impaired by use of morphine-like drugs during parturition; the neonate appears to be particularly susceptible to respiratory depression induced by opioids in part due to a poorly developed blood-brain barrier (Reisine and Pasternak, 1996). In humans, opioids cause vasodilation of cutaneous vessels, probably due to histamine release. Allergic phenomena in general (including bronchoconstriction), and those manifested in skin, may be exacerbated with opioid use if morphine-like drugs are used. Pruritis may occur, in part due to histamine, but also due to direct effects on neurons (Reisine and Pasternak, 1996). Opioids appear to inhibit cytotoxic activity of natural killer cells. Selected opioid compounds, however, appear to enhance macrophage and killer cell activity, possibly through a novel opioid receptor (Reisine and Pasternak, 1996; see Chapter 19).

Changes in body temperature reflect altered thermoregulatory response. Hypothermia is more common in dogs, whereas hyperthermia is more common in cats (Branson et al., 1996).

Drug Interactions

The depressant effects of opioids can be exacerbated by other CNS depressants. Several CNS depressants prolong the effects of opioids, including the phenothiazines and tricyclic antidepressants. Although some phenothiazines may reduce the amount of opioid necessary for analgesia, others may increase the amount of opioid (Reisine and Pasternak, 1996).

POWERFUL PURE AGONISTS

Morphine

Morphine (0.25 to 5.0 mg/kg intramuscularly [IM], subcutaneously [SC] every 4 hours, dog [D]; 0.1 mg/kg IM, SC, intravenously [IV] every 4 hours, cat [C]) is considered the prototypic narcotic. A class II drug, morphine targets primarily mu and to a lesser degree delta and kappa receptors. Morphine causes profound sedation and analgesia for up to 6 hours in the dog. Its effects are reversed with narcotic antagonists. Morphine can cause cardiac depression (Napier, 1999); in addition, hypotension may reflect histamine release or CNS (vasomotor) depression (Robinson, 1988; Hakim, 1992). Morphine can cause respiratory depression (Cullen, 1999), particularly in neonates (Luks, 1998), and can cause acute pulmonary edema due to histamine release (Hakim, 1992). Therapeutic uses include premedication for surgical anesthesia (reducing the amount of other potentially nonreversible CNS depressants) and analgesia. Morphine is also used in cases of acute, fulminating pulmonary edema because of its ability to reduce cardiac preload due to hepatic venous constriction and splanchnic pooling.

Morphine has been used orally by humans, although first-pass metabolism requires oral doses that are two to six times parenteral doses. Its major metabolite in humans is a glucuronide metabolite (morphine-6-glucuronide), however, whose pharmacologic action is equal to that of the parent compound. Although the metabolite is more potent than morphine, it is not as able to cross the blood-brain barrier (Reisine and Pasternak, 1996). With chronic morphine dosing, as drug concentrations accumulate, it is likely that the metabolite contributes more than morphine to control of pain, suggesting that oral administration may be effective for dogs. Marked variability among human patients in the rate of morphine metabolism complicates establishment of the best oral dose in the individual patient. Morphine has not been used orally for animals because of its poor oral bioavailability, although doses are provided for a slow release preparation. The formation and importance of morphine-6-glucuronide has not been established for animals. Morphine has been studied in dogs using several routes. Median peak concentrations were 0.92 ng/mL and 182 ng/mL 5 minutes after administration of 0.5 mg/kg IV and 2 mg/kg IM (Barnhart, 2000) compared to a targeted range of 9 to 39 ng/mL for analgesic efficacy in humans. Bioavailability of IM morphine is high (119%) but variable (57–161%), and elimination half-life approximates 90 minutes. Vomiting occurred following IV and IM (5/6 dogs) administration at these doses (mean morphine concentration at vomiting of 66 ng/mL) and heart rates were significantly lower. Following rectal administration, morphine is approximately 20% bioavailable, achieving peak concentrations of 28 ng/mL when 2 mg/kg is administered as a solution and 20, 21, and 51 ng/mL when administered as a suppository at 1, 2, and 5 mg/kg, respectively. Elimination half-life (minutes) ranged from 65 (solution) to 98 (suppository). Vomiting was common (5/6 animals) with a 5 mg/kg recal suppository. Alternative morphine formulations have been studied in dogs in an attempt to provide longer analgesia with fewer side effects. Morphine has been studied subcutaneously prepared as a solution (Tasker, 1997) and as a sustained-release gel (N,O-carboxymethylchitosan polymer) product (Tasker, 1997) and when given orally (Dohoo, 1997). Following subcutaneous injection at 1.2 mg/kg, peak concentrations for the solution and sustained product were 488 and 180 ng/mL, respectively, with time to peak concentrations being 10 and 55 minutes, respectively. Variability among animals was large. Elimination half-life was 79 (solution) and 108 (gel) minutes. Oral administration of 15 mg (approximately 1.7 mg/kg) revealed peak morphine concentrations of 20 to 24 ng/mL occurring at 2 to 3 hours. Elimination half-life appeared to approximate 2.5 hours leading to a 12-hour dosing interval recommendation. Morphine also has been studied following epidural administration of the solution (0.1 mg/kg) (Robinson, 1999) and as a sustained-release encapsulated preparation (experimental; 10 and 30 mg in 3 mL saline) (Yaksh, 1999). Both appear to prolong analgesia while avoiding side effects.

Morphine has been used in the dog and cat effectively as a premedicant or a perioperative analgesic (Branson et al., 1996). In dogs, following subcutaneous administration, peak effects occur by 45 minutes. Duration of analgesia is reported to be between 1 to 2 hours, but clinically appears longer. Emesis should be anticipated (Branson et al., 1996). A variety of routes of administration for morphine are listed in Table 22–2. Morphine can be administered safely epidurally (preparations made specifically for epidural ad-

Table 22–2. Doses of Drugs Used to Control Pain*

Opioid analgesics	
Buprenorphine	0.005–0.03 mg/kg IV, IM, SC (D) 0.005–0.01 mg/kg IM, IV (C)
Butorphanol	0.2–1.0 mg/kg IM, SC, IV every 3–6 h (D) 0.2–1 mg/kg PO every 1–6 h (D) 0.1–1.0 mg/kg every 12 h (C) 0.4 mg/kg (as reversal agent)
Codeine	1.0–4.0 mg/kg every 6 h
Codeine with acetaminophen	1–2 mg/kg every 6 h (D) (based on codeine)
Fentanyl	0.04–0.08 mg/kg IM, SC, IV every 2 h (D) 0.005–0.04 mg/kg IV every 0.5–1.0 h (D) 0.005–0.04 mg/kg epidural
Fentanyl transdermal patch	Apply 12–24 h before need for 72–120 h analgesic relief 5–10 kg, 25 μg/h 10–20 kg, 50 μg/h 20–30 kg, 75 μg/h >30 kg, 100 μg/h
Meperidine	2–10 mg/kg IM every 2 h (D); 2–4 mg/kg IM every 2 h (C)
Morphine	0.1–0.5 mg/kg IM, SC every 4 hrs (D) 0.3–3.0 mg/kg PO every 4–8 h (D) 0.05–0.5 mg/kg PO every 4–8 hours (C) 0.5–2.5 mg/kg sustained release PO every 8–12 h 0.1 mg/kg IM, SC, IV every 4 h (C) 0.1–1.0 mg/kg PO every 4–8 h (C) 0.1–0.5 mg/kg/h IV continuous infusion
Nalbuphine	0.1–1.0 mg/kg IM, IV every 1–6 h (D)
Naloxone	0.04 mg/kg IM, SC, IV every 2 h or PRN (D, C); dilute dose to 10 mL with saline
Opioid analgesics *Continued*	
Nalorphine	11–22 mg/kg every 2–3 h IM, SC, IV (D); dilute dose to 10 mL with saline
Oxymorphone	0.02–0.2 mg/kg IM, SC, IV, every 2–6 h, <60 mg total (D) 0.02–0.1 mg/kg IM, SC, IV every 2–6 h (C)
Pentazocine	2–3 mg/kg IM every 2 h (D) and every 4–5 h (C)
Adjuvant analgesics	
Acepromazine	0.02–0.10 mg/kg IV, SC
Amitriptyline†	2.2–4.4 mg/kg PO every 24 h (D), 5–10 mg/kg PO (C)
Diazepam	0.1–0.2 mg/kg IV
Imipramine†	2.2–4.4 mg/kg PO every 12–24 h (D)
Ketamine	1–2 mg/kg IV (for burns), 0.5–1.0 mg/kg IM (C)
Methocarbamol	0.55–2.2 mL/kg PO (D, C)
Midazolam	0.1–0.2 mg/kg IV, IM
Xylazine	0.05–0.2 mg/kg IV, IM
Epidural or regional analgesics	
Bupivacaine	0.2 mL/kg of 0.5% solution (epidural) 0.5 mL for intercostal nerve block every 6–8 h 1.5 mg/kg intrapleural every 3–12 h (maximum of 4–5 mg/kg [D], 2–3 mg/kg [C])
Buprenorphine	0.005 mg/kg, dilute in saline 1 mL/5 kg
Morphine	0.1–0.3 mg/kg preservative free (D) epidural every 4–8 h
Lidocaine	0.2 mL/kg
Morphine	0.01 mg/kg
Oxymorphone	0.1 mg/kg

C = cat; D = dog; IM = intramuscular; IV = intravenous; PO = oral; PRN = as needed; SC = subcutaneous.
*Doses are those currently recommended for young adult animals. Doses have not been modified to compensate for age.
†Dose for behavioral disorders.

ministration are preferred) and appears to be effective when given either epidurally (Day et al., 1995; Pascoe and Dyson, 1993) or locally (intra-articularly) (Day et al., 1995) for control of some orthopedic pains.

Fentanyl

Fentanyl (0.04 to 0.08 mg/kg IM, SC, IV every 2 hours [D]) is a synthetic opioid (Class II) with a potency 100 times that of morphine and 500 times that of meperidine; hence doses are lower. It interacts with mu receptors (more so than morphine) and to a lesser degree with delta and kappa receptors. Fentanyl is most commonly recognized as a drug used to induce neuroleptanalgesia (when combined with droperidol). After parenteral administration, however, it causes profound sedation and respiratory depression. Auditory sensitization and altered thermoregulation (leading to panting) may occur. Pretreatment with atropine is indicated when administering the drug parenterally. Because it undergoes redistribution (as with thiobarbiturates), repetitive administration may result in accumulation of the drug in fat and prolonged duration of effect. Despite redistribution, the short half-life of fentanyl previously has limited its use to IV infusion. Fentanyl is now, however, available as a transdermal drug delivery system intended for control of pain (Fig. 22–4). This method of drug delivery has proved safe and effective for delivery of fentanyl to both dogs and cats.

The transdermal drug delivery system provides slow, continuous drug delivery that is intended to provide a fairly constant plasma fentanyl concentration. Peak and trough concentrations, which might cause toxicity and therapeutic failure, respectively, are thus avoided. The fentanyl transdermal patch system has been approved for control of cancer pain in people. The system consists of a patch comprised of an adhesive layer that attaches to the skin. A "release" membrane controls the rate of release of drug from the reservoir. Because the amount of drug that is released is proportional to the size (area) of the patch, the "dose" is the amount of drug (in micrograms) released per unit time (hour). The system is available in four sizes: 25, 50, 75, and 100 μg/h. Note that because of the relationship between skin and patch and because of the different characteristics of the skin between dogs (or cats) and people, the rate of drug delivery (and elimination from the skin) is different.

The fentanyl patch has been studied in dogs (Kyles et al., 1996; Egger et al., 1998) and cats. With the 50 μg/h patch, drug delivery approximated 37 μg/h (range of 13.7 to 59.8 μg/h) in dogs, and the patch was found to be an effective means of constant, slow drug delivery. Peak concentrations occur within 24 hours in the dog and can occur in as few as 3 to 5 hours in the cat. A comparison of

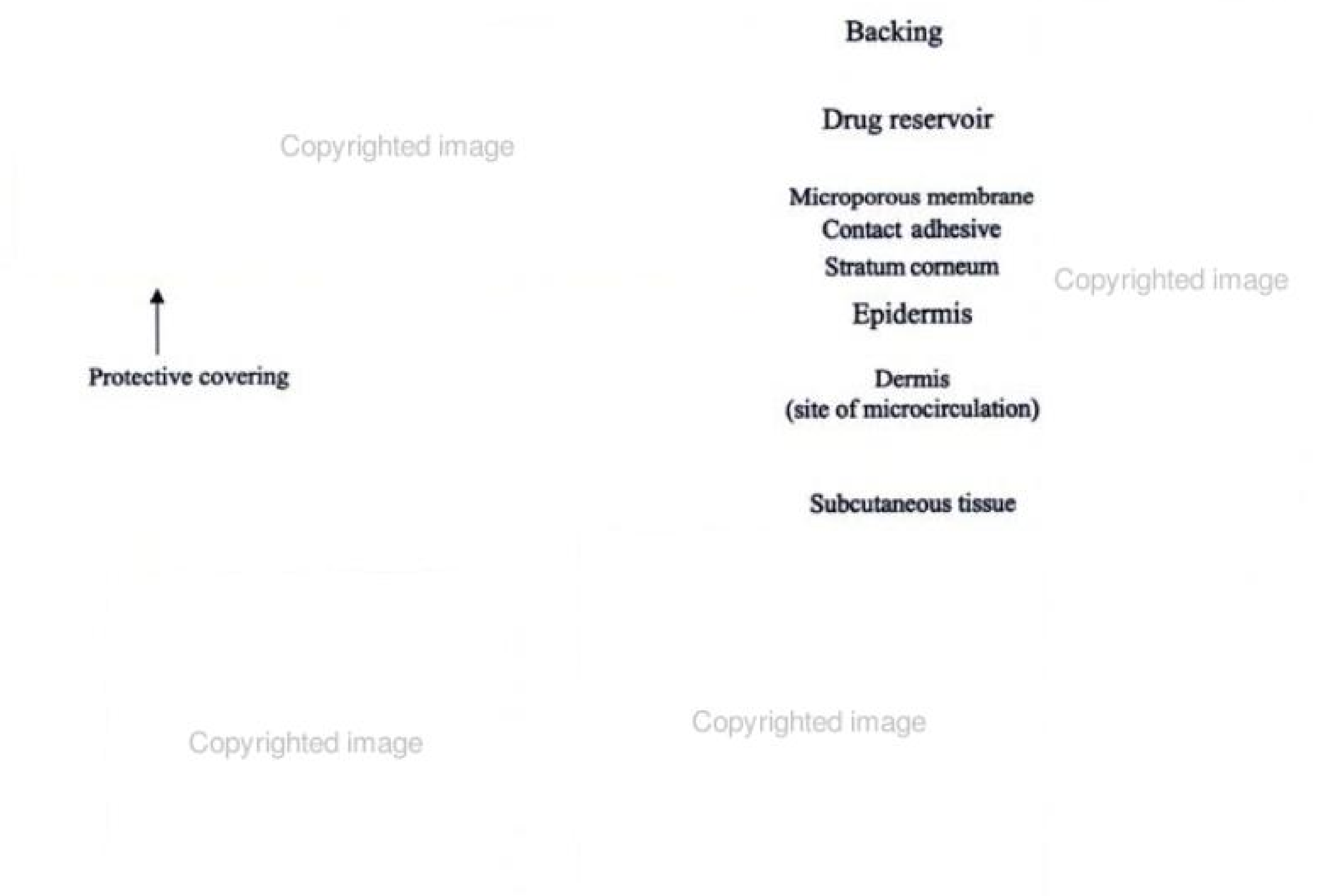

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Figure 22–4. The transdermal fentanyl patch system. The dermis is the site of microcirculation and thus drug absorption.

Meperidine reduces the heart rate and systemic arterial pressure in dogs due, in part, to peripheral vasodilation. Bronchoconstriction also occurs in the dog. It is a potent initial stimulant of the gastrointestinal tract. Rapid intravenous injection can cause peripheral vasodilation. Diphenoxylate (the active opioid ingredient in Lomotil) is a derivative of meperidine.

MILD TO MODERATE PURE AGONISTS

Codeine

Codeine is 60% bioavailable in humans after oral administration. Although effective concentrations reach circulation after oral administration, the potency of codeine as an analgesic is less than that of morphine. Codeine has a very low affinity for opioid receptors, and its analgesic effects are due to metabolism (demethylation) to morphine (Reisine and Pasternak, 1996). Only a small percent (10%) of morphine is formed, however, and its antitussive effects probably reflect direct interaction with codeine receptors (Reisine and Pasternak, 1996). In dogs, even less codeine appears to be converted to morphine. Its antitussive effects require lower plasma drug concentrations than expected for analgesia. Currently, its primary indication for small animals is as a cough suppressant (2.2 mg/kg [D]) or antidiarrheal. Outpatient use of this drug as an analgesic, particularly when combined with a non-narcotic analgesic (i.e., nonsteroidal anti-inflammatories or acetaminophen) is increasing. Codeine is scheduled as Class II.

Miscellaneous Drugs

Oxycodone (Percodan, Class II), *hydrocodone* (Hycodan, Class III), and *propoxyphene* (Darvon, Class IV) are used to variable degrees in veterinary medicine. Among them, hydrocodone is most commonly used for suppression of cough. *Diphenoxylate* (Class II as a sole agent; when combined with atropine to control substance abuse as Lomotil, Class V) is used to control diarrhea because of its effects on the gastrointestinal tract. *Loperamide* is similar to diphenoxylate, but it does not penetrate the blood-brain barrier as effectively, and hence is associated with no CNS side effects.

MIXED AGONISTS AND ANTAGONISTS

Butorphanol

Butorphanol (0.4 to 0.8 mg/kg IM, SC, IV every 3 to 6 hours [D, C]; oral [antitussive in dog]: 0.5 to 1.0 mg/kg every 12 hours; recently scheduled as Class IV) is a kappa agonist and a mu antagonist. It is three to five times more potent (agonist) than morphine and about 50 times *less* potent than naloxone as an antagonist. Butorphanol has been used as both a preanesthetic and a perioperative analgesic in dogs and cats. It is one of the three most commonly used opioids for control of postoperative pain in small animals (Dohoo and Dohoo, 1996; Hubbell and Muir, 1996), the other two being buprenorphine and oxymorphone (Hansen and Hardie, 1993). It is also used (approved) as an antitussive (Christie et al., 1980). Although butorphanol does cause respiratory depression, a ceiling apparently is reached beyond which additional dosing does not cause further depression (a mu antagonist) (Hosgood, 1990). Butorphanol causes less biliary spasm than does morphine, supporting butorphanol's postoperative use (Roebel et al., 1979). It is also used as an antitussive in small animals.

Peak analgesia occurs in 30 to 60 minutes, and in dogs the half-life is 1.65 hours (Pfeffer et al., 1980). Analgesic effects can last up to 4 to 6 hours in some animals. In dogs, however, duration of analgesia may be as little as 30 to 60 minutes after IV administration (Houghton et al., 1991) or SC administration (Sawyer et al., 1991). Butorphanol appears to be safe in cats if used cautiously (Sawyer and Rech, 1987). At high doses, butorphanol provides some relief of somatic pain. Butorphanol may be an effective analgesic for mild to moderate pain. Butorphanol had enjoyed until recently a nonschedule designation by the Food and Drug Administration, but it was recently designated as class IV. For postsurgical pain, butorphanol should be administered 10 minutes before the end of surgery. The oral preparation of the drug has been dispensed for 1 to 2 days in patients released from the hospital; higher oral doses compared with parenteral doses are required because of its reduced bioavailability after oral administration (0.5 to 1.0 mg/kg every 12 hours). Butorphanol may act synergistically when combined with acetaminophen for control of pain (Pircio et al., 1978). Although safe, epidural administration of butorphanol does not provide sufficient duration of action to be clinically useful (Troncy et al., 1996).

Butorphanol (0.4 mg/kg) can be used to partially reverse the sedative or respiratory depressant effects of oxymorphone (Dyson et al., 1990) (and presumably other pure opioid agonists). Some of the analgesic effects of the pure opioid will also, however, be reserved.

Buprenorphine

Buprenorphine (0.005 to 0.03 mg/kg IV, IM, SC, epidural [D]) is a Class V thebaine derivative with potent analgesic effects 25 or more times greater than that of morphine (Heel et al., 1979). It is a kappa antagonist and a mu partial agonist/antagonist (Romero et al., 1989). Buprenorphine is one of the three most commonly used opioids for control of pain in small animals (Watson et al., 1996; Dohoo and Dohoo, 1996; Hubbell and Muir, 1996), and it has been recommended as the most generally useful analgesic for controlling pain in laboratory animals (including dogs) (Flecknell, 1984). Although its onset of action is longer than that of morphine, its effects last much longer (in humans). In dogs, buprenorphine appears to have a 42-hour half-life (Garrett and Chandran, 1990). Because of its high lipophilicity, buprenorphine has a very high volume of distribution (33 L/kg) and appears to be sequestered in tissues. The long half-life may contribute to its longer duration of action compared with butorphanol.

Like morphine, buprenorphine induces dose-dependent respiratory depression, which may be delayed in onset;

like butorphanol, a ceiling is reached. Although respiratory depression has not been a problem in human patients receiving the drug, it is noteworthy that these effects are not fully reversible with antagonists such as naloxone. Cardiovascular side effects are limited. The cat may respond to buprenorphine with mydriasis and agitation at doses more than 0.2 mg/kg. An added advantage of buprenorphine is its ability to reverse opioid-induced sedation while maintaining analgesia. It has been recommended as the reversal agent of choice (i.e., in lieu of naloxone) for human patients receiving neuroleptanalgesics.

Pentazocine

Pentazocine (2 to 3 mg/kg IM every 2 hours [D] or every 4 to 5 hours [C]) induces analgesia that is one third as potent as morphine. It is not, however, associated with as severe cardiovascular and respiratory depression. It is effective only as a visceral analgesic. Its utility is limited by its short duration of activity (30 minutes) and by its tendency to cause undesirable behavior (Sawyer and Rech, 1987).

Nalbuphine

Nalbuphine is a nonscheduled opioid that was at one time used as an analgesic for small animals. It is a mu receptor antagonist and kappa receptor agonist with minimal cardiovascular effects. Butorphanol and buprenorphine have largely replaced the use of this drug.

NARCOTIC ANTAGONISTS

Antagonists are used to provide quick reversal in the event of an overdose or serious respiratory depression or if ambulation is desirable after use of an opiate. Depending on the antagonist and the receptors with which it interacts, analgesia will be reversed along with the undesirable side effects. This is particularly true of pure antagonists. Like agonists, antagonists can be considered pure or partial in their effects. Antagonists generally are not scheduled.

Naloxone

Naloxone (0.04 mg/kg IM, SC, IV every 2 hours or as needed [D, C]; dilute dose in 10 mL of saline and administer to effect IV; give remaining dose SC) is a pure antagonist with 30 times the potency of nalorphine and 50 times the potency of butorphanol. It is approved for use in the dog but not the cat. As a pure antagonist, it is not regulated by the Controlled Substances Act. Its ability to block each of the opioid receptor types varies; indeed, receptor type can be based somewhat on response to naloxone. Mu receptors are the most sensitive to naloxone antagonism, sigma receptors the least. High doses of naloxone will reverse both delta and kappa receptors. Reversal with naloxone also depends on the affinity for naloxone and the target receptor being greater than that of the drug to be reversed and on the receptor. Among the opioids, buprenorphine is characterized by a very high affinity for receptors that exceeds that of naloxone; thus, buprenorphine is not reversible by naloxone.

After successful reversal with naloxone, respiratory, sedative, and cardiovascular effects of opioids are reversed for 1 to 4 hours. Repeat administration may be indicated, depending on which opioid agonist was used. For example, the effects of oxymorphone may last longer than those of naloxone (Copeland et al., 1989). Naloxone should be administered slowly when given as an IV bolus because of possible cardiovascular stimulation that manifests as increased sympathetic nervous system activity (Michalis et al., 1974). The increased sympathetic nervous system activity presumably reflects the sudden reversal of analgesia and thus the perception of pain. In human beings, this increased sympathetic nervous system activity may be demonstrated as tachycardia, hypertension, pulmonary edema (Flacke et al., 1997; Tanaka, 1974), and cardiac dysrhythmias (including ventricular fibrillation).

Naloxone antagonizes the effects of nonopiate depressants as well as alters dopamine and γ-aminobutyric acid actions in the CNS (Branson et al., 1996). It has also been studied for its ability to alter detrimental physiologic response in circulatory and septic shock; however, this therapeutic use, which was once considered a benefit, appears to provide no decrease in mortality and may cause detrimental effects.

Naloxone is not approved as a reversal agent in cats, and cats do not appear to react predictably to reversal with naloxone. Recovery and survival was not improved in kittens in which opioids were reversed (Faggella and Aronsohn, 1993).

Nalorphine

Nalorphine is a partial agonist and as such is a class III drug. Sedation and analgesia are maintained, and CNS (including respiratory) depression is reduced.

Nalbuphine

Nalbuphine (Nubain) (1 mL of 20 mg/mL solution to 9 mL saline, as with naloxone) is discussed as a mixed agonist/antagonist. Like, butorphanol and buprenorphine, nalbuphine has been used as a partial antagonist to induce reversal of CNS depression but not as an analgesic.

Naltrexone

Naltrexone is an orally bioavailable pure antagonist that has been used to treat lick granulomas in dogs.

THERAPEUTIC USE OF OPIOID ANALGESICS

Opioids are used in veterinary medicine to control pain; as adjuvant anesthesia, emetics (apomorphine), antitussives, and antidiarrheals; and for chemical restraint. In 1954, the optimum dose of opioids as defined in human medicine

opioids. α_2-Agonists are also indicated, although sedative and cardiovascular effects limit their use to epidural administration or as part of combination therapy. General anesthesia alone may not be sufficient to control intraoperative analgesia.

Several opioid analgesics are useful for the control of surgical pain. For animals suffering pain before surgical induction, oxymorphone or butorphanol administered as part of a preanesthetic or anesthetic regimen can both control pain and reduce the amount of general anesthetic. Likewise, animals to be subjected to a surgical procedure that will induce pain that is not likely to be successfully controlled with general anesthetics will also benefit from presurgical administration. Meperidine is generally used as a preanesthetic to minimize the amount of general anesthetic needed for a geriatric or debilitated (e.g., poor cardiovascular system) animal rather than to control pain. In addition, a fentanyl patch can be applied the day before surgery. Opioids might also be given intraoperatively if cardiovascular signs indicate the perception of pain despite a general anesthetic. Agents that can be reversed or those with a ceiling effect should be used to minimize the risk of respiratory or cardiovascular depression.

Postoperatively, any of the opioids can be administered, and the selection should be based on the degree of analgesia desired balanced with the risk of sedation in the postoperative patient. Those most commonly selected by small animal practitioners include oxymorphone, buprenorphine, and butorphanol (Hansen and Hardie, 1993; Dohoo and Dohoo, 1996; Hubbell and Muir, 1996). Severe pain indicates the need for pure agonists such as morphine or oxymorphone. Less severe pain may sufficiently respond to buprenorphine or butorphanol. Of the two, buprenorphine can be expected to consistently provide a longer period of analgesia (about 4 to 6 hours). Acepromazine can be combined with either butorphanol or buprenorphine for sedation. Pulse oximetry can be used to evaluate tissue oxygenation and the potential risk associated with a sedating drug, including a pure agonist opioid.

The sedative effects of the opioid may be desirable for some patients but undesirable for others. An advantage to these drugs is that the sedating effects can be reversed if necessary. Note, however, that repeated administration of the reversing agent may be necessary (e.g., naloxone). Alternatively, if a sedating opioid has been used and reversal of the sedating effects is desirable, butorphanol or buprenorphine can be used. A portion of the analgesic effect will also be reversed (because of antagonistic actions at mu receptors for both of these drugs), but kappa receptors will mediate some analgesia. Fentanyl transdermal patches can be applied postoperatively, but it is likely that the analgesic effects of the patch will need to be supplemented short term.

Nonsteroidal anti-inflammatory drugs (NSAIDs) can be very effective postoperatively; in addition to their peripheral anti-inflammatory effects, NSAIDs may have central actions as well. Care should be taken with the use of NSAIDs; drugs that are selective for COX2 are preferred (see Chapter 16). Carprofen is among the most effective and safest drugs used perioperatively. Although ketorolac and flunixen meglumine are NSAIDs characterized by analgesia that approximates that provided by morphine, neither drug is relatively COX2 selective, and side effects should be anticipated. Ketoprofen and ketorolac also have been used to control postoperative pain, with variable effects (Mathews et al., 1996) (see Chapter 16). Fluid therapy during surgery is important to prevent renal complications, and excessive bleeding may occur due to inhibition of thrombogenesis. Combinations of opioids (codeine, butorphanol) and NSAIDs or acetaminophen should be considered in order to avoid the side effects associated with NSAID use.

Critically Ill Patients

Stress that is too severe can complicate the care of the critically ill patient. Invasive procedures intended to support the patient produce pain that can be severe, requiring use of sedation, local analgesics, or central analgesics. Procedures that require some type of analgesic therapy include placement of urinary, nasal, and nasogastric catheters; bone marrow aspiration; and drainage or lavage of body cavities. Opioid sedation, or a combination of ketamine (100 mg/mL) and diazepam (5 mg/mL) mixed 1 to 1 and administered at 0.05 to 0.1 mL/kg may limit stress associated with these procedures (Anthony, 1995; Murtaugh and Kaplan, 1996).

Among the opioids most commonly used to control pain beyond that associated with supportive procedures are morphine, oxymorphone, and butorphanol (Hansen and Hardie, 1993). Side effects of most concern include respiratory and cardiac depression. Most animals can, however, tolerate mild respiratory depression associated with opioids, and respiratory disease or trauma is not a contraindication for opioid use in animals. For example, morphine can be used for the patient with pulmonary edema secondary to heart failure. In addition to splanchnic pooling and decreased preload to the heart, sedation decreases struggling and oxygen use. Morphine can be given to effect at 0.1 mg/kg every 3 minutes until light sedation has been achieved. Oxymorphone may be the preferred opioid of choice for animals for which systemic hypotension can be life threatening because it is less likely to cause histamine release. Fluid therapy is indicated if hypotension occurs (Anthony, 1995; Murtaugh and Kaplan, 1996).

The use of local anesthetics for the critically ill patient, should not be ignored. The short duration of action of lidocaine leads to its usefulness for short invasive procedures. It has been used intravenously in human patients as a centrally acting analgesic, but in animals it should be administered in conjunction with another analgesic if used centrally (1 to 2 mg/kg loading dose followed by continuous IV infusion at 25 to 40 μg/kg per minute. The longer duration of action of bupivacaine lends itself to control of pain associated with surgery or trauma. Bupivacaine can be infiltrated in the proximal intercostal nerves for surgical procedures or infiltrated through a chest tube (0.25% to 0.5%, up to 1 to 2 mg/kg every 6 hours) for control of thoracic pain. Sufficient drug can be absorbed to induce toxicity after local administration. Bupivacaine is more cardiotoxic than lidocaine and cardiac depression is more likely with repeated administration. Central nervous system reactions include depression and stupor, which may precede seizures. Epinephrine can be used to slow absorption of

these drugs may be more appealing for the patient with cranial trauma. Buprenorphine, however, has both mu (supraspinal) agonistic and antagonistic effects, whereas butorphanol only antagonizes mu receptors. In addition, buprenorphine is not fully reversible at mu receptors and therefore should probably be avoided until the traumatized patient has been completely stabilized. Once the risk of degrading mental status is minimal, buprenorphine will be safer. Pure opioid agonists such as morphine and oxymorphone can be used, but these drugs are more likely to contribute to CNS depression induced by trauma. An advantage to either of these drugs, however, is their full reversibility by opioid antagonists. Should reversal be indicated, extra caution should be taken to ensure slow reversal, thus avoiding a hyperanalgesic response and its physiologic sequelae. In addition, care should be taken to assess the need for repeated administration of the reversal agent (Dewey et al., 1997; Bullock and Ward, 1995).

Direct depression of the respiratory centers, coupled with decreased responsiveness to arterial P_{CO_2}, are likely to be exacerbated in the patient with cranial trauma. Lung volume decreases in the normal patient, and depression of the cough reflex (especially morphine) increases aspiration of accumulated secretions and development of atelectasis due to retention of respiratory secretions. Respiratory rate, depth, and rhythm should be closely monitored during opioid administration. Blood gases should be monitored in patients at risk for respiratory depression. Although pulse oximetry can confirm tissue oxygenation, tissue P_{CO_2} drives respiratory rate and cerebral vascular responses. Respiratory acidosis may develop despite normal tissue oxygenation. Increased P_{CO_2} can lead to increased cerebral blood flow, which may exacerbate cerebral hemorrhage. In addition to effects of cerebral vasculature, the respiratory rate may be altered (slowed). In a patient whose respiratory center is threatened as a consequence of cranial trauma, further suppression of the respiratory center by an opioid can be life threatening. Drugs characterized by a ceiling effect on respiratory depression (e.g., butorphanol and buprenorphine) will decrease, but not exclude, the risk of opioid-induced CNS respiratory depression. The use of continuous epidural opiate infusions is recommended for human patients that have sustained multiple pulmonary trauma (Dewey et al., 1997; Bullock and Ward, 1995).

Cardiovascular depression is also a concern in the patient with cranial trauma receiving opioid analgesics. Depression can be mediated through the central centers, directly on the myocardium, or due to peripheral effects (particularly opioids such as morphine that mediate histamine release). Again, close monitoring of rate, rhythm, and pulse is indicated during the initial stages of opioid use. Oxymorphone and fentanyl, which are not associated with as much histamine as is morphine, might be preferred over morphine (Dewey et al., 1997; Bullock and Ward, 1995).

Epidural Analgesia

Epidural administration of analgesics can be used to facilitate anesthesia for surgery or to provide prolonged postoperative analgesia. For analgesic effects, opioids are most useful. Opioids cause selective spinal analgesia by binding to opioid receptors in the dorsal horn of the spinal cord segments. The processing of signals sent by nociceptors is modulated. Thus, central effects are absent. Opioids most commonly administered epidurally include morphine, oxymorphone, buprenorphine, and fentanyl. The specific opioid to be used depends on the targeted region. Pelvic analgesia can be provided by a number of opioids; for abdominal or thoracic analgesia, a drug with a low lipid solubility, (e.g., morphine) is indicated to allow more time for cranial diffusion (after lumbosacral administration) before the dura is penetrated. Morphine also has the longest onset of action (up to 90 minutes) but provides the longest duration of analgesia (up to 24 hours). When used to control postoperative pain, it should be administered before surgery. Fentanyl is very lipid soluble. Its analgesia is very rapid in onset, but does not extend more than one to two spinal cord segments from the injection site. Its central effects are more common than those of other analgesics because of its high lipid solubility and rapid absorption into systemic circulation. It can be combined with morphine to provide analgesia as the morphine penetrates the dura.

Pruritus is a common side effect in human patients receiving opioids epidurally. Delayed respiratory depression is a complaint in a much smaller percentage of the human population. Neither of these side effects has been reported in animals. Because opioids cause no paralysis, there is little to no loss of skeletal muscle (motor) function. Weakness of the detrusor muscle and urine retention are not, however, unusual. Among the opioids, buprenorphine appears the least likely to cause urinary retention. Catheterization may be necessary in some patients.

Local anesthetics provide direct anesthesia at any nerve root with which the drug comes in contact. This effect is spinal if the drug is administered into the cerebrospinal fluid. Bupivacaine is more potent and lipid soluble than lidocaine yet has a slower onset of action and longer duration of effect. Motor blockade should be anticipated but can be minimized by use of dilute concentrations (0.0625% to 0.125%). An opioid can be used for diluting bupivacaine 1 to 1 up to 1 to 3 (by volume).

Epidural administration of analgesics is contraindicated for patients with neurologic deficits or injuries and coagulopathies, bacteremia, and severe systemic infections. Despite the lack of reported toxicity, drugs that contain preservatives (such as multiple dose vials) should be avoided because they may contain preservatives that are neurotoxic. The risk of toxicity increases with multiple injections. Products containing sodium metabisulfite should not be administered intrathecally. The use of epinephrine in combination with local anesthetics and, in particular, bupivacaine also should be avoided because of very prolonged (24 to 48 hours) muscle weakness. Potential complications of epidural analgesia include epidural or intrathecal hemorrhage, spinal nerve root trauma, motor blockage (particularly with local anesthetics), central effects as the drug diffuses to the brain, and weakness or ataxia.

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Anesthetic Agents

23

Elizabeth A. Martinez

PREANESTHETIC MEDICATIONS
Introduction
Anticholinergics
  General Pharmacology
  Atropine Sulfate
  Glycopyrrolate
Tranquilizers
  Acepromazine
  Diazepam
  Midazolam
Opioids
α_2-Adrenergic Agents
INJECTABLE ANESTHETICS
Introduction
Barbiturates
Dissociative Agents
Propofol
Etomidate
INHALANT ANESTHETICS
Introduction
Nitrous Oxide
Methoxyflurane
Halothane
Isoflurane
Sevoflurane
Desflurane

PREANESTHETIC MEDICATIONS

Introduction

The use of preanesthetic medications before general anesthesia in dogs and cats has several advantages. The advantages include helping to decrease stress and anxiety, providing analgesia, decreasing the amount of subsequent anesthetic drugs used, and minimizing the cardiopulmonary depression associated with the commonly used anesthetic agents.

The preanesthetic medications used routinely in dogs and cats include the anticholinergics, phenothiazine and benzodiazepine tranquilizers, opioids, and α_2-adrenergic agonists. Certain drugs discussed in this chapter are not labeled for dogs or cats or for the dose and route of administration suggested. Decisions regarding extra-label use should be based on the judgement of the veterinarian and the current laws governing extra-label use of drugs.

Anticholinergics

General Pharmacology

Anticholinergics competitively antagonize acetylcholine at postganglionic terminations of cholinergic fibers in the autonomic nervous system. They are used as preanesthetic medications to decrease salivary secretions, decrease gastric fluid acidity, and inhibit the bradycardic effects of vagal stimulation. Other effects include mydriasis, decreased tear formation, decreased intestinal motility, and bronchodilation. Atropine sulfate and glycopyrrolate are the two anticholinergic drugs used for dogs and cats.

Atropine Sulfate

Atropine sulfate (0.02 to 0.04 mg/kg) can be administered intramuscularly (IM), subcutaneously (SC), or intravenously (IV). The duration of action is 60 to 90 minutes. Atropine may stimulate vagal nuclei in the medulla and cause an initial bradycardia before the desired effect is seen. Other central effects of atropine include depression, restlessness, and delirium. Atropine administration may cause cardiac arrhythmias and sinus tachycardia. Atropine does cross the placental barrier and may lead to central and peripheral anticholinergic effects in the fetus when administered to the dam. Arrhythmias are more common after IV administration and include second-degree atrioventricular block, unifocal ventricular premature contractions, and ventricular bigeminy (Thurmon et al., 1996).

Glycopyrrolate

Glycopyrrolate is a synthetic quaternary ammonium anticholinergic. Glycopyrrolate may be given IM, SC, or IV at a dose of 0.011 mg/kg. The duration of action is 2 to 4 hours, significantly longer than that of atropine. The cardiovascular effects of glycopyrrolate are similar to those of atropine. Glycopyrrolate, due to its large structure, does not cross the blood-brain or placental barrier readily and therefore has minimal central or fetal effects (Muir and Hubbell, 1995).

Tranquilizers

Acepromazine

Acepromazine (0.05 to 0.1 mg/kg IV, IM, SC, not to exceed a total dose of 3 mg), a phenothiazine tranquilizer, is used commonly as a premedication before general anesthesia in dogs and cats to relieve anxiety. Through depression of the reticular activating system and antidopaminergic actions in the central nervous system (CNS), acepromazine produces mental calming, decreased motor activity, and increased threshold for responding to external stimuli. Acepromazine does not produce analgesia but may act synergistically when administered concurrently with other drugs with analgesic activity.

Administration of acepromazine will decrease the dose of subsequent anesthetic agents. Other effects include antiemetic activity, antihistaminergic properties, and lowering of the seizure threshold. Hypotension and hypothermia can occur because of depression of vasomotor reflexes. Acepromazine is metabolized by the liver and should not be used in patients with liver disease. Because of the potential for hypotension, acepromazine should be used cautiously in compromised patients, particularly those with significant cardiovascular disease. Acepromazine may inhibit platelet function and should be avoided in patients with coagulopathies (Muir and Hubbell, 1995).

Diazepam

Diazepam (0.1 to 0.2 mg/kg IV) is a benzodiazepine tranquilizer that possesses muscle relaxant and anticonvulsant properties. Benzodiazepines exert their effect by enhancing the CNS inhibitory neurotransmitters γ-aminobutyric acid (GABA) and glycine and by combining with CNS benzodiazepine receptors (Thurmon et al., 1996). Diazepam may produce a mild calming effect in some patients, but agitation and excitement can also occur. Diazepam is solubilized by mixing with propylene glycol. Diazepam has minimal cardiovascular effects; bradycardia and hypotension may occur after rapid IV administration. Propylene glycol is associated with pain upon injection and incompatibility when mixed in the same syringe with other drugs. Clinical uses of diazepam in small animal anesthesia include providing muscle relaxation when given concurrently with dissociative anesthetics and as a coinduction agent with injectable anesthetics (e.g., thiopental, propofol, etomidate) to decrease their dose or side effects. The effects of diazepam can be reversed with the benzodiazepine antagonist flumazenil.

Midazolam

Midazolam (0.05 to 0.1 mg/kg IV, IM) is a benzodiazepine tranquilizer with behavioral effects and clinical uses similar to diazepam. Midazolam is more potent and has a shorter duration of action than diazepam. Midazolam is water soluble at pH 3.5. At a pH above 4.0, the chemical structure changes to become lipid soluble (Ilkiw, 1992). Unlike diazepam, midazolam can be mixed with other anesthetic agents and can be administered IM without causing irritation. Flumazenil can be used to antagonize midazolam's effects.

Opioids

Opioids act by combining with one or more specific receptors in the brain and spinal cord to produce analgesia, sedation, euphoria, dysphoria, and excitement. The μ receptors are thought to mediate supraspinal analgesia, respiratory depression, and euphoria. Kappa receptors mediate spinal analgesia, miosis, dysphoria, and sedation, and the sigma receptor mediates hallucinations, psychomimetic activity, and respiratory and vasomotor stimulation. Delta receptors are thought to primarily modify mu receptor activity (Thurmon et al., 1996). Opioids are classified as agonists, agonists/antagonists, or antagonists according to their receptor activity (see Chapter 22).

Agonist and agonist/antagonist opioids are used before, during, and after surgery in dogs and cats to provide analgesia. Certain opioids may produce sedation in some patients. The antagonists are used to reverse the effects of the agonists or agonists/antagonists. The opioid chosen is based on the degree and duration of expected pain and physical status of the patient. Understanding the differences between the commonly used opioids and their possible side effects is also important when choosing which drug to use. Dose, route, classification, and duration of action of the commonly used opioids for dogs and cats are listed in Table 23–1.

α_2-Adrenergic Agents

The α_2-adrenergic agonists are used to produce sedation, muscle relaxation, and analgesia in dogs and cats by stimulating presynaptic α_2-adrenoreceptors, which causes a decrease in norepinephrine release both centrally and peripherally. This action leads to a decrease in both CNS sympathetic outflow and circulating catecholamines (Muir and Hubbell, 1995). Cardiopulmonary effects can be significant with these drugs and include respiratory depression, bradycardia, first-degree or second-degree atrioventricular blockade, decreased cardiac output, and increased peripheral vascular resistance. Because of these effects, careful patient monitoring should be employed after administration in dogs and cats. The use of α_2-adrenergic agonists in compromised patients should be avoided.

The two most commonly used drugs are xylazine and medetomidine. Xylazine (0.2 to 1.0 mg/kg IV, IM) can be given as a premedication agent alone or in combination with opioids. It is also used commonly as an adjuvant with

Table 23–1. Commonly Used Opioids for Dogs and Cats

Opioid	Dose (mg/kg)	Route	Duration of Action	Classification
Morphine	0.05--1.0	IM, SC	4 h	Agonist
Oxymorphone	0.05–0.1	IV, IM, SC	4 h	Agonist
Butorphanol	0.2–0.4	IV, IM, SC	2 h	Agonist/antagonist
Buprenorphine	0.005–0.015	IV, IM, SC	6–8 h	Agonist/antagonist
Fentanyl	0.005–0.01	IV, IM	20–40 min	Agonist
Nalbuphine*	1.0	IV to effect	NA	Agonist/antagonist
Naloxone	0.04–0.06	IV to effect	NA	Antagonist

Abbreviations: IM = intramuscular; IV = intravenous; SC = subcutaneous.

*Nalbuphine is used to reverse the sedative effects of opioid agonists without affecting analgesia.

dissociative anesthetic agents to improve muscle relaxation and provide visceral analgesia. Medetomidine (cat, 40 to 80 μg/kg IV, IM; dog, 10 to 40 μ/kg, IV, IM) is the newest α_2-agonist approved for veterinary use. The user is advised to consult the package insert for specific dosing recommendation of medetomidine for dogs. Although the clinical effects are similar, medetomidine is more potent and possesses a higher α_2-receptor selectivity profile than xylazine. Profound bradycardia is common after medetomidine administration but can be minimized by preemptive treatment with an anticholinergic agent.

Reversal of the clinical effects of xylazine and medetomidine can be accomplished with specific α_2-adrenergic antagonists. Yohimbine HCl (0.1 mg/kg IV), tolazoline (2 mg/kg), and atipamezole are most commonly used in dogs and cats. Atipamezole is used to reverse the effects of medetomidine. The manufacturer's package insert has specific dosing guidelines.

INJECTABLE ANESTHETICS

Introduction

Injectable anesthetic agents are used to rapidly produce unconsciousness. Most often they are given before maintenance of general anesthesia with an inhalant anesthetic agent but may also be administered by repeated injection or infusion, alone or in combination with other injectable agents, to maintain anesthesia. The major disadvantage of injectable agents is that, once administered, the effects are not immediately eliminated, including any unwanted cardiopulmonary changes. The injectable agents used for veterinary patients include the barbiturates, dissociative agents, propofol, and etomidate.

Barbiturates

The barbiturates cause depression of the CNS by interfering with the passage of impulses to the cerebral cortex. Barbiturates are categorized according to their duration of action. The ultrashort-acting barbiturates thiopental and methohexital are the two most commonly used for dogs and cats to produce a rapid induction of anesthesia. The transition to inhalant anesthesia is smooth, and recovery is relatively rapid due to redistribution. Methohexital is cleared from the body at a faster rate and is preferred for sighthounds, which have a more prolonged recovery with the thiobarbiturates.

The barbiturates decrease cerebral blood flow, cerebral metabolic rate of oxygen, and electrical activity of the brain (Muir and Hubbell, 1995). Because of these CNS effects, anesthetic induction with a barbiturate is preferred for patients with certain neurologic diseases (seizure disorders, space-occupying lesion of the brain). Other organ system effects include cardiovascular and respiratory depression that is dependent on the dose and rate of administration. Cardiac arrhythmias may occur, with ventricular extrasystoles and bigeminy being the most common (Muir and Hubbell, 1995).

Maximal effect from an IV injection of an ultrashort-acting thiobarbiturate is reached within 30 seconds. The duration of action depends on redistribution to lean body tissues. Barbiturates are primarily metabolized by the liver and eliminated by renal excretion. Care should be taken when administering barbiturates to patients with liver disease, as the duration of action may be prolonged.

Thiopental can be used as a 2% to 5% solution for dogs and cats. More concentrated solutions may cause severe tissue damage if accidently administered perivascularly. For induction of anesthesia, thiopental is administered in small increments, 2 to 6 mg/kg IV, until the desired effect is reached. A total dose of 10 to 12 mg/kg is usually sufficient for induction, before intubation and maintenance with an inhalant agent. Repeated injections of thiopental for maintenance of anesthesia have a cumulative effect and can cause a prolonged recovery.

Methohexital is similar in its effects to thiopental except that it is more rapidly metabolized and is not cumulative (Muir and Hubbell, 1995). Methohexital is reconstituted as a 2.5% solution, and a calculated dose of 6 to 10 mg/kg is drawn up in a syringe. One-half is administered initially, and the remainder is given to the desired effect. In unpremedicated patients, involuntary excitement or emergence delirium can be seen during the recovery period. Treatment is accomplished with administration of diazepam, 0.2 mg/kg IV.

Dissociative Agents

Dissociative anesthesia is an anesthetic state caused by interruption of ascending transmission from the unconscious to conscious parts of the brain (Lin, 1996). This group includes ketamine and tiletamine. Tiletamine is a component of TELAZOL. Dissociative anesthesia is characterized by catalepsy; somatic analgesia; and intact ocular, laryngeal, and pharyngeal reflexes. Control of the airway may not be complete; therefore, intubation with a cuffed endotracheal tube is recommended. Visceral analgesia is poor. Muscle rigidity or reflexive skeletal muscle movements can also occur. Dissociative agents are used commonly for induction and maintenance of anesthesia in cats and dogs.

Both ketamine and tiletamine increase cerebral blood flow and intracranial pressure and therefore should be avoided for patients in which these effects could be detrimental (Lin, 1996). Seizure activity may be seen, particularly in dogs. Due to sympathetic stimulation, the cardiovascular effects include an increase in heart rate and arterial blood pressure. The myocardium becomes sensitized to catecholamine-induced arrhythmias. Although ventilation and arterial oxygenation generally remain adequate, an apneustic or irregular breathing pattern may be observed after administration of a dissociative agent. Transient apnea may be seen after rapid intravenous administration. Excessive salivation can occur and is controlled by administration of an anticholinergic. Hallucinatory behavior, emergence delirium, or CNS excitement may be observed during the recovery period. Prior administration of a tranquilizer will attenuate these effects.

Although ketamine is metabolized primarily by the liver in the dog, it is excreted intact by the kidneys in the cat.

Ketamine should be used with caution in animals with hepatic or renal disease. In cats with urethral obstruction, ketamine can be used if renal disease is absent and the obstruction is relieved. Tiletamine is excreted predominantly by the kidneys. Telazol is contraindicated in patients with pancreatic disease or impairment of renal function.

Ketamine can be administered IV (1 to 2 mg/kg) or IM (2 to 20 mg/kg) for induction or maintenance of anesthesia in cats and dogs. Intravenous administration is used for induction before intubation and maintenance with an inhalant agent or for anesthesia in short procedures. Intramuscular administration, in combination with agents providing analgesia and muscle relaxation (i.e., xylazine), is used for maintenance of anesthesia in surgical procedures. Duration of action is dose dependent. Recovery from large IM doses of ketamine may be associated with prolonged recoveries. Ketamine should be combined with a tranquilizer, muscle relaxant, or opioid to provide muscle relaxation and additional analgesia and to ease the recovery period. Using adjuvants is important when administering ketamine to dogs because, when used alone, extreme muscle tone, spontaneous movements, violent recovery, and convulsions can occur.

TELAZOL is a combination of tiletamine and zolazepam. Tiletamine has a longer duration of action and greater analgesic effect than ketamine. Zolazepam, a benzodiazepine tranquilizer, provides muscle relaxation and is an effective anticonvulsant. TELAZOL has been used IM (4 to 15 mg/kg), alone or in combination with xylazine or an opioid, for induction and maintenance of anesthesia in surgical procedures. Lower doses (2 to 4 mg/kg) can be given intravenously for induction before intubation and maintenance with an inhalant agent. Adverse responses to TELAZOL can occur during the recovery period, particularly in dogs. These responses include muscle rigidity, convulsions, and emergence delirium. Using the lowest dose of TELAZOL possible and treatment with a tranquilizer will minimize these effects.

Propofol

Propofol (2,6-diisopropylphenol) is classified as a nonbarbiturate sedative/hypnotic agent. It is an alkylphenol, is poorly soluble in water, and is solubilized in a lecithin-containing emulsion (Intralipid). Propofol emulsion is capable of supporting microbial growth, and therefore unused propofol, in either an ampule or vial, should be discarded within 6 hours. The advantage of propofol over other injectable anesthetic agents is its rapid recovery profile (Branson and Gross, 1994).

Propofol causes a decrease in both intracranial and cerebral perfusion pressures and therefore can be used in patients with neurologic disease. Propofol has cardiovascular effects similar to the thiobarbiturates, including a dose-dependent decrease in arterial blood pressure, cardiac output, and systemic vascular resistance. Heart rate may remain unchanged or increased. Ventricular arrhythmias may also be observed. Propofol should be used with caution in patients with severe cardiovascular disease. Propofol does cause a dose-dependent respiratory depression and may also cause transient apnea. Methods for ventilatory support should be available.

Propofol is noncumulative. Termination of the anesthetic effects from propofol is due to redistribution from vessel-rich tissues followed by rapid biotransformation by the liver. Propofol is rapidly cleared from the body by hepatic and extrahepatic metabolism.

Propofol can be administered as an IV bolus (4 to 6 mg/kg) for induction of anesthesia as well as maintenance of anesthesia by a constant-rate infusion (0.4 mg/kg per minute). Propofol does not provide analgesia; therefore, painful procedures should not be performed when given alone. Premedication with an opioid or α_2-agonist will provide analgesia, but dose requirements for propofol will be lowered. Propofol allows for a rapid recovery with little to no hangover effect compared with the thiobarbiturates. Side effects include excitement during induction or recovery in unpremedicated patients, pain on injection, and occasional muscle tremors or myoclonic activity (Smith et al., 1993). The main disadvantages of propofol are cost and limited shelf life.

Etomidate

Etomidate is an imidazole derivative classified as a rapid-acting, nonbarbiturate anesthetic agent (Muir and Mason, 1989). It is not a good analgesic. Etomidate (1 to 3 mg/kg) is used as an IV induction agent before intubation and maintenance with an inhalant agent. The main advantage of etomidate over other injectable induction agents is its minimal cardiopulmonary depressant effects, and therefore it is very useful for severely compromised patients.

Etomidate is a good induction agent for neurologic procedures because it depresses cerebral blood flow and cerebral metabolic rate of oxygen. Administration of etomidate produces little change in heart rate, arterial blood pressure, and cardiac output. Transient apnea may be observed after induction. In unpremedicated patients, administration of etomidate may be associated with pain on injection, involuntary muscle movements, gagging, or retching (Muir and Mason, 1989). Prior premedication with a tranquilizer and/or opioid will attenuate these effects. Etomidate causes transient adrenocortical suppression (Kruse-Elliot et al., 1987). The effects may be seen for 2 to 3 hours after a single IV bolus. Although it is thought that this suppression is not clinically significant after a single dose, long-term infusion with etomidate is not recommended. Etomidate is noncumulative, is rapidly redistributed, and undergoes some ester hydrolysis.

INHALANT ANESTHETICS

Introduction

Inhalant anesthetic agents are used to produce general anesthesia in dogs and cats. These drugs produce unconsciousness, muscle relaxation, and analgesia. Inhalant anesthetic agents are administered directly to the respiratory system, absorbed from the alveoli into the bloodstream, and passed to the brain. The advantage of using inhalant

Anticonvulsants and Other Neurologic Therapies in Small Animals

24

Dawn Merton Boothe

INTRODUCTION
PATHOPHYSIOLOGY OF SEIZURES
PRINCIPLES OF ANTICONVULSANT THERAPY: PHARMACOKINETIC CONSIDERATIONS
THERAPEUTIC DRUG MONITORING
GENERAL COMMENTS REGARDING THE USE OF ANTICONVULSIVE DRUGS
Acute Management
Chronic Control
Drugs Contraindicated for Epileptic Patients
ANTICONVULSANT DRUGS
Phenobarbital
  Mechanism of Action
  Disposition
  Preparations
  Clinical Use
  Drug Interactions
  Side Effects
  Treatment of Acute Phenobarbital Toxicosis
Primidone
  Side Effects
  Drug Interactions
Phenytoin Sodium
  Pharmacologic Activity
  Disposition
  Clinical Use
  Drug Interactions
  Blood Concentrations and Associated Toxicity
  Other Side Effects
Benzodiazepines: Diazepam, Clorazepate, Clonazepam, and Lorazepam
  Mechanism of Action
  Disposition
  Preparations
  Safety
  Therapeutic Use
  Use in Treatment of Status Epilepticus
  Use in Chronic Therapy
Clonazepam
Bromide
  Preparations and Sources
  Mechanism of Action
  Disposition
  Side Effects
  Therapeutic Use
Felbamate
Gabapentin
Valproic Acid
Mephenytoin
Pentobarbital Sodium
TREATMENT OF OTHER NEUROLOGIC CONDITIONS
Brain Trauma or Injury
  Pathophysiology of Brain Injury
  Causes of Severe Brain Injury
  Cerebral Edema
  Increased Intracranial Pressure
  Medical Management
Acute Thoracolumbar Disc Extrusion
  Medical Management
  Glucocorticoids and Other Anti-inflammatory Drugs

INTRODUCTION

Successful control of seizures with anticonvulsant drugs reflects a balance in achieving seizure control while minimizing undesirable drug side effects (Parent, 1988). Variability in the disposition of anticonvulsants and interactions among them are important confounders of successful therapy. This chapter reviews selected anticonvulsants, focusing on drugs most likely to control seizures in small animals. The proper use of anticonvulsants is discussed, with an emphasis on the differences in individual drug disposition, detection of these differences, and rational approaches to responding to these differences by dose modification. The primary topic of discussion is treatment of generalized, tonic-clonic seizures, the most common type afflicting small animals. Opinions regarding anticonvulsant therapy vary among clinicians. Most of the comments and recommendations offered in this discussion reflect personal observations in a therapeutic drug monitoring service and completed as well as ongoing clinical trials that focus on the use of anticonvulsants either alone or in combination with phenobarbital.

It is important to approach epilepsy as a clinical manifestation of an underlying disease. Thus, therapy is more likely to be effective if the underlying disease is treated. Such causes should be identified and appropriately treated before chronic anticonvulsant therapy is instituted. Neutering of animals (male and female) is strongly encouraged not only for ethical reasons but also to minimize the potential adverse effect of circulating sex hormones on neuronal membrane stability. Unfortunately, the underlying cause of disease often cannot be identified (idiopathic epilepsy) or treated such that seizures are adequately controlled. Regardless of the cause of seizures in such cases, management is based on control of seizures with anticonvulsant drugs. Undesirable side effects are often the limiting factor in the use of anticonvulsant drugs, and not all seizures necessarily need to be treated.

Certainly immediate, short-term anticonvulsant therapy is indicated for status epilepticus (see later definition) or cluster seizures. Chronic therapy is generally indicated for seizures that last more than 3 minutes, cluster seizures (for which there is no delineable interictal period), or seizures that occur more frequently than once a month. Seizures that are not sufficiently controlled can lead to additional seizuring (kindling) or to the development of a second "mirror" focus of seizure activity. This might be manifested as a decreasing interictal period or a worsening of seizure activity (including duration).

PATHOPHYSIOLOGY OF SEIZURES

The normal resting membrane potential (RMP) of the neuronal cell is −70 mV. The electrical difference across the cell membrane is maintained by an Na^+,K^+-ATPase pump. Depolarization and the generation of an action potential occurs when the RMP becomes sufficiently positive to reach threshold. As with other membranes, the RMP of a neuron is determined by the concentration of negative and positive ions across the membrane. Important ions include Na^+,K^+,Ca^{2+}, and Cl^-. The concentration reflects ion fluxes and thus permeability of the cell membrane to the ions. Fluxes resulting in an increase in positive ions inside the cell relative to the outside hypopolarize the RMP, bringing it closer to threshold and subsequent depolarization. The tendency of a neuron to depolarize reflects, in part, the sum total effect of neurotransmitters (NTs), which interact with the cell membrane. Inhibitory NTs such as γ-aminobutyric acid (GABA) render the RMP more negative and less susceptible to depolarization (Fig. 24–1) (Loscher, 1993). Excitatory NTs such as acetylcholine and glutamate elevate the RMP to a more positive status, rendering it more susceptible to reaching the threshold necessary for depolarization (Loscher, 1993). Glutamate receptors can initiate seizures experimentally; antagonism of *N*-methyl-D-aspartate (NMDA) receptors antagonizes the excitatory effects (Rogawski, 1992; Whetsell, 1996).

Seizures are the clinical results of rapid, excessive neuronal discharge in the brain. Seizures are classified as primary (i.e., genetic) or acquired and as generalized or focal. Generalized seizures are much more common in small animals; the incidence is greater in dogs than in cats. With seizure onset of a generalized character, convulsive electroencephalographic activity begins simultaneously in all brain regions (Faingold et al., 1985). Many seizures in epileptic subjects have been attributed to a cortical origin. There is increasing evidence, however, that the brain stem can exhibit self-sustained seizure discharge, and this area of the brain may serve an important role in the generation and expression of generalized tonic convulsions (Browning, 1985). Within the brain stem, the pontine reticular formation is believed to play a key role in the generation or expression of tonic convulsions or both. Studies indicate that the ability to depress reticular core activity is an essential characteristic of antiepileptic drugs and suggests that the reticular formation is involved in the spread and generalization of clinical seizures (Fromm, 1985).

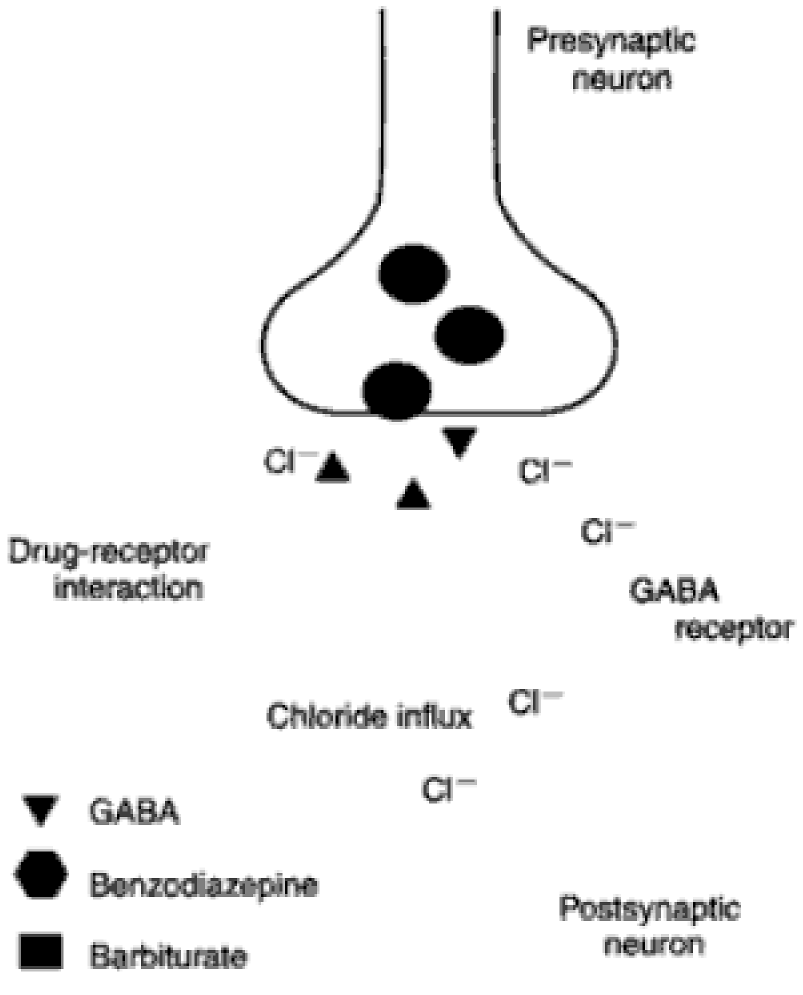


Figure 24–1. The receptor for γ-aminobutyric acid (GABA) has binding sites for GABA, barbiturates, and benzodiazepines. Interaction between the drug and receptor causes a channel in the receptor to open to chloride flux. Increased chloride concentrations inside the cell increase electronegativity, thus hyperpolarizing the cell.

In the dog, the most common form of epilepsy is generalized tonic-clonic or grand mal seizures (Cunningham, 1984; Schwartz-Porsche et al., 1985). Epilepsy or seizure disorders of the central nervous system (CNS) in the dog may be caused by an acquired organic lesion such as brain tumor, head trauma, toxicosis, electrolyte imbalance, hypoglycemia, renal failure, or hepatic disease (acquired or secondary epilepsy) or may be genetic or inherited ("true," idiopathic, or primary epilepsy). An autosomal gene associated with a sex-linked suppressor on the X chromosome may explain the higher incidence of seizures in male dogs.

Status epilepticus refers to failure of the patient to recover to a normal alert state between repeated tonic-clonic attacks or episodes that last at least 30 minutes (Delgado-Escueta et al., 1982). Convulsive or tonic-clonic status epilepticus is a medical emergency in which convulsive seizures must be terminated by treatment with anticonvulsant agents. In humans, epileptic seizures must not be allowed to persist more than 60 minutes if severe, permanent neurologic injury or death is to be avoided (Delgado-Escueta et al., 1982). The longer an epileptic seizure persists, the greater the incidence of mortality and morbidity. Hyperthermia due to continuous muscle contraction may become life threatening during continued seizure activity. Brain damage due to hypoxia or to the sequelae of hyperthermia is more likely if more than 30 minutes of uninterrupted seizures occur.

Seizures can be initiated by four general mechanisms: (1) altered neuronal membrane function, which can lead to excessive depolarization (e.g., alteration of the Na^+,K^+ pump; permeability changes in the cell membrane induced, for example, by hypoxia, inflammation, or trauma); (2) decreased inhibitory NTs, such as GABA, the most potent inhibitory NT in the CNS (see Fig. 24–1); (3) increased excitatory NTs, such as glutamate; and (4) altered extracellular potassium and calcium concentration (Loscher, 1993; Stringer, 1998). Imbalances between excitatory and inhibitory NTs have been suggested as a cause of epilepsy; indeed, in dogs with spontaneous idiopathic epilepsy, increased glutamate concentrations and decreased GABA concentrations have been reported (Podell and Hadjiconstantinou, 1997), providing a rational target for drug therapy. During a seizure, extracellular potassium increases and calcium decreases, which increases neuronal excitability and facilitates the initiation and spread of the seizure. Once initiated, the seizure discharge may synchronize with other neurons and propagate to surrounding areas in the brain. Anticonvulsants block seizure initiation and propagation by blocking abnormal events in a single neuron or the synchronization of related neurons. Drugs acting at more than one point (e.g., phenobarbital) tend to be most effective. Alternatively, combination therapy with drugs that

life. In contrast to its metabolism rate in people, phenytoin is very rapidly metabolized in dogs (half-life less than 2 hours).

One sequela of phase I metabolism may be activation to a compound of equal, greater, or less anticonvulsant efficacy than that of to the parent drug. Primidone must be metabolized to its active metabolite phenobarbital before it is effective in dogs. Clorazepate, a benzodiazepine, is also a pro-drug derivative, but it is converted in the stomach to its active metabolite. Although diazepam is rapidly metabolized, its duration of pharmacologic effect is prolonged because most of its metabolites have some degree of anticonvulsant effect (Fig. 24–3). The half-life of the metabolites may also be longer than those of the parent compounds.

The safety of anticonvulsant drugs is profoundly affected by metabolism. Phase I metabolites, by their nature, are reactive. Although intended to progress to phase II metabolism, some reactive metabolites can interact with and damage surrounding tissues, which, for hepatically metabolized drugs, is the liver. Thus, hepatotoxicity may be a common and predictable side effect of long-term anticonvulsant use. The larger the dose and the greater the amount of drug metabolized, the greater the potential toxicity.

In addition to causing hepatotoxicity, any drug metabolized by the liver can potentially affect drug-metabolizing enzymes, and drug interactions are a common sequela of anticonvulsant therapy. The type of interaction is difficult to predict and varies with each drug combination. Phenobarbital is the most potent hepatic drug-metabolizing enzyme inducer known. The rate of drug metabolism will increase clearance, and (assuming patient volume of distribution does not change) the elimination half-life of many drugs subsequently will decrease if a patient receives continuous phenobarbital therapy. Phenobarbital increases its own rate of metabolism, and therefore drug concentrations of phenobarbital can be expected to decrease in patients receiving long-term therapy without changing (decreasing) the dose. A dose increase should be anticipated in patients after 3 to 6 months; monitoring should be used to guide the dose increase. Phenytoin is another potent enzyme inducer. It also can decrease the drug concentration of phenobarbital when the two drugs are given in combination. It can also compete with phenobarbital for metabolism, however, resulting in an increase in the concentration of one or the other drug. Thus, the effects of the two drugs when given in combination are not predictable. Clorazepate increases concentrations of phenobarbital (reason unknown); this effect is more likely to be clinically detectable when plasma concentrations of phenobarbital are high (>35 μg/mL) and a high dose of clorazepate is given (2 mg/kg) (D.M.B., personal experience).

Note that drugs that impair or inhibit drug-metabolizing enzymes will also impact anticonvulsant therapy if the anticonvulsant is metabolized by the liver. Cimetidine, ketoconazole, and chloramphenicol are drugs that decrease drug metabolism and thus potentially increase concentrations of the anticonvulsant. Chloramphenicol can increase phenobarbital concentrations more than 30% in as little as 2 days, leading to unexpected and potentially profound grogginess (D.M.B., personal experience).

Hepatic metabolism of anticonvulsants also impacts the efficacy of anticonvulsant therapy. The relationship between the dosing interval of an anticonvulsant and the rate of elimination affects therapeutic success. This relationship is explained more in depth in Chapter 1. The rate of elimination is reflected in the drug elimination half-life ($t_{1/2}$), the time necessary for 50% of the drug to be eliminated at steady state. The dosing interval is generally based on an acceptable level of fluctuation between peak and

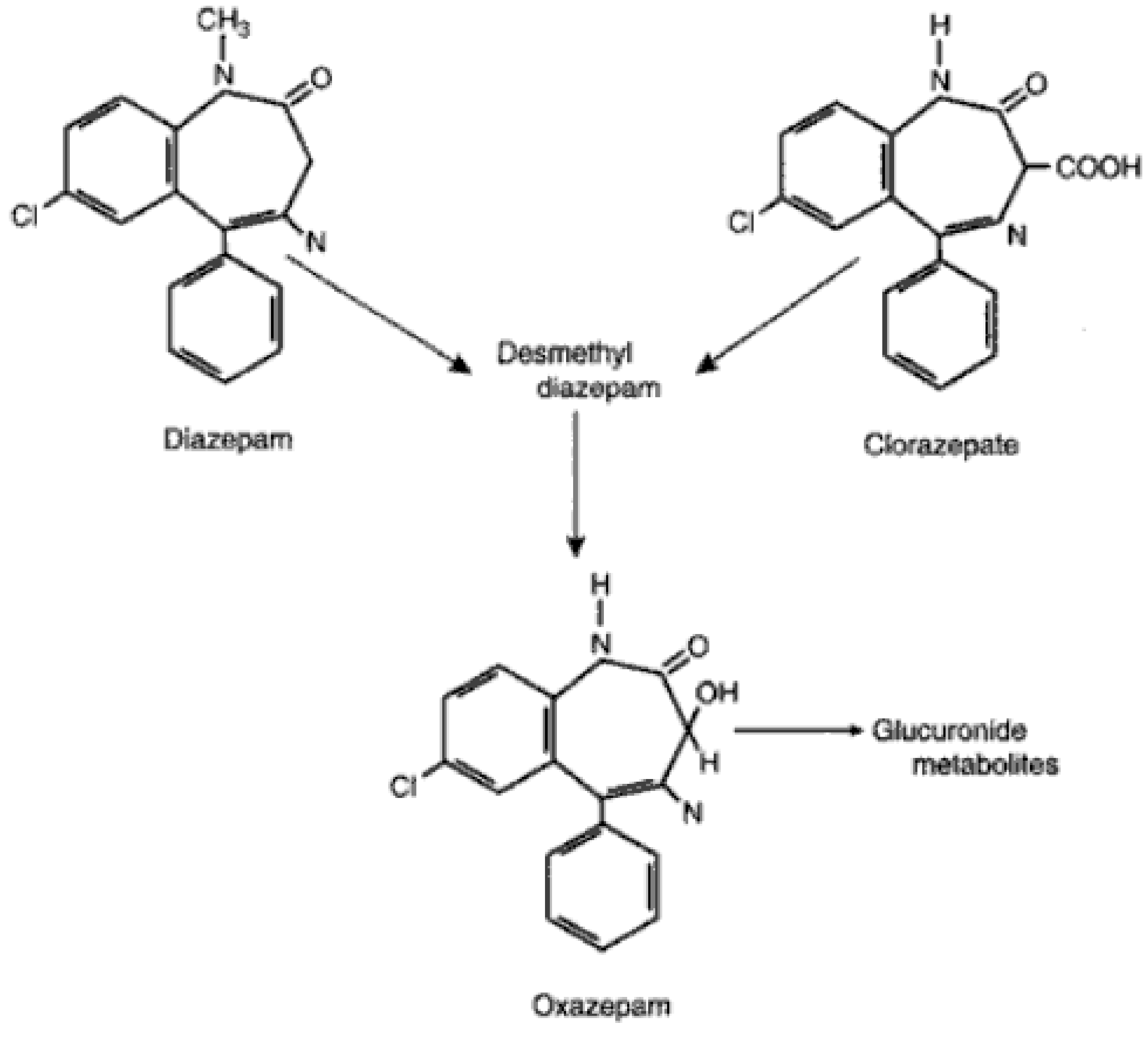


Figure 24–3. Phase I metabolism of diazepam yields metabolites of active, although less potent, metabolites. Clorazepate is metabolized in the stomach. Desmethyl diazepam = nordiazepam.

ously, with a drug that accumulates, the time to reach steady-state concentration can be several days to several weeks, depending on drug half-life. The time to steady state and therapeutic response may be unacceptably long for patients suffering from severe, life-threatening seizures. For such patients, a *loading dose* can be administered to achieve therapeutic anticonvulsant concentrations immediately or within the first few days of therapy. In brief, the loading dose is a sum of all the daily doses that would have been administered before steady state minus any drug that would have been eliminated from the body during that time period. The major disadvantage of a loading dose is the sudden effect of therapeutic concentrations in the CNS; there is no time for adaptation to occur, and adverse effects (sedation, ataxia) are more likely than with gradual increases in drug concentrations. The maintenance anticonvulsant dose that follows the loading dose is designed to replace drug eliminated during a dosing interval, thus maintaining therapeutic concentrations achieved by the loading dose. Both the loading and maintenance doses are, however, based on population disposition parameters. Yet individual differences in drug elimination may result in therapeutic failure with either dosing regimen.

Therapeutic drug monitoring (TDM) can be used to document these differences and to guide modification of the maintenance dose. Generally, monitoring is recommended after the loading dose is completed, and to ensure that the maintenance dose is correct, at one drug elimination half-life. This second time is selected because, if the maintenance dose does not maintain what is achieved with the loading dose, the majority of the change as a new steady state is reached will occur during the first half-life of the drug. Thus, for bromide in particular, a maintenance dose can be changed proactively at 3 weeks after the loading dose rather than waiting for the risk of seizures or marked sedation at 3 months as the new steady state is finally reached.

THERAPEUTIC DRUG MONITORING

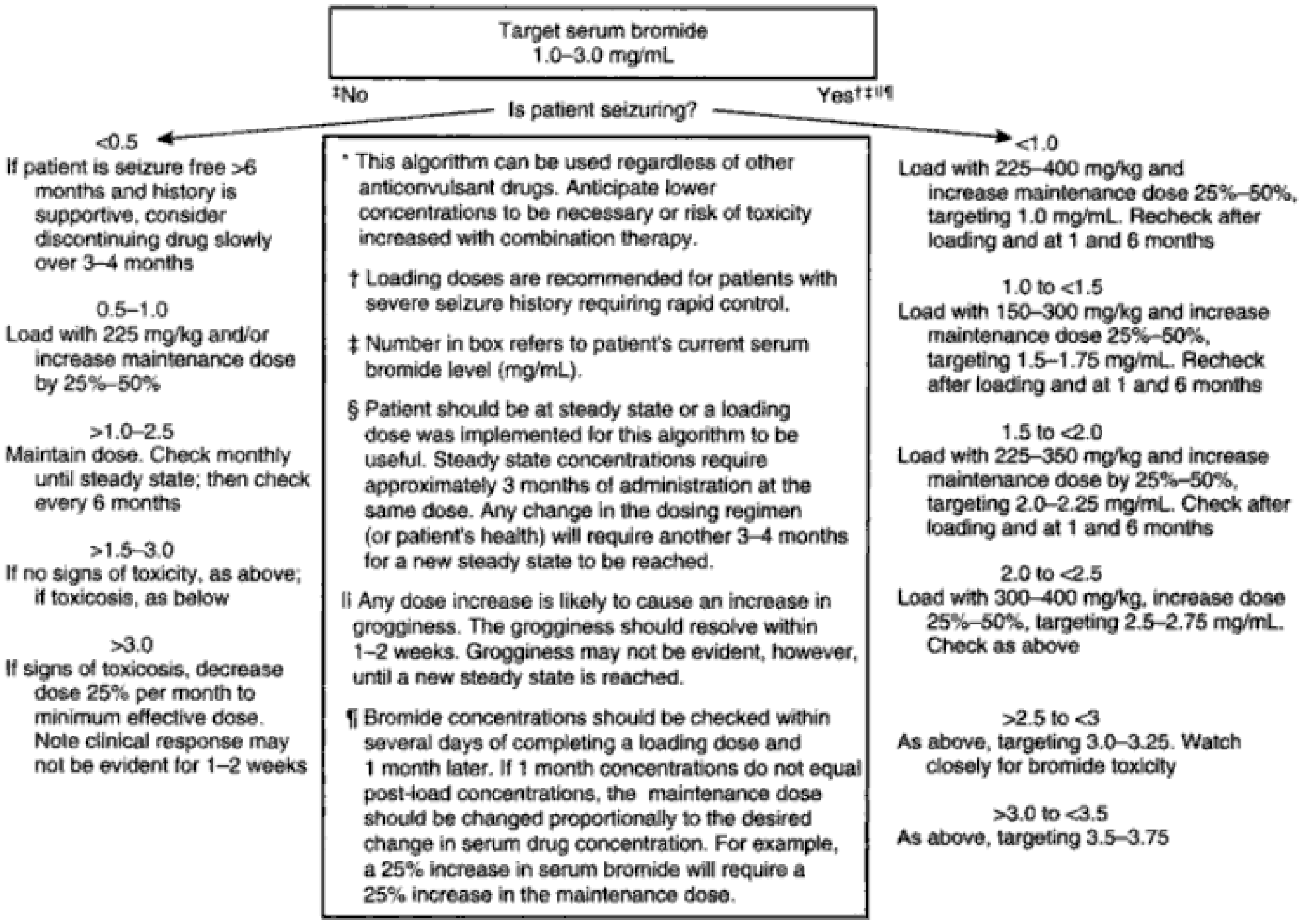
Therapeutic drug monitoring can be a powerful tool for controlling the difficult epileptic animal. Unfortunately, not all anticonvulsant drugs can be monitored (see Chapter 4). A therapeutic range must be established for the drug, and response must correlate with plasma drug concentrations. An easy, cost-effective assay that requires minimal sample handling must be available. Among the anticonvulsants to be discussed, automated assays are available for phenobarbital (also used for primidone) and the benzodiazepines. Bromide can also be assayed, although the tedium of the assay limits the number of laboratories that offer this service.

Drug concentrations should be monitored after a loading dose, one drug elimination half-life later, and intermittently (e.g., including baseline and a 3- to 6-month interval) at steady state. Monitoring is indicated whenever the dose is changed (at the new steady state) or when the patient seizures. If drug half-life is substantially longer than the dosing interval (we recommend greater than 3 times), peak and trough concentrations will be very similar, and a single trough sample collected just before a dose is sufficient. Thus, for bromide and in patients for whom phenobarbital is characterized by a long half-life (i.e., induction has been minimal), a single trough sample is sufficient. We recommend a trough rather than a peak sample because of less variability at this time compared with peak times. Usually, both phenobarbital and bromide can be measured in the same sample. On the other hand, if the dosing interval is equal to or greater than 50% of the drug half-life, both peak and trough samples should be collected to document the proximity of plasma drug concentrations to toxic and subtherapeutic concentrations and to calculate half-life so that the dosing interval can be modified if necessary. Thus, for the benzodiazepines or for phenobarbital in patients for whom induction has occurred, we recommend both a peak and a trough sample.

Note that induction by phenobarbital cannot be detected without a peak and a trough sample (a sort of catch 22: one must collect both a peak and a trough sample to make sure that subsequent monitoring can consist of a trough alone). For peak samples, we recommend collection at 4 to 5 hours after the dose, followed by a trough sample just before the next dose. A less accurate but more convenient schedule is collection of a trough sample before the morning dose and a peak sample 5 hours after the dose. The time of sample collection in relationship to dose administered before both peak and trough sample collection must be known if the half-life is to be calculated. We recommend that animals fast before samples are collected. Special handling preparation is not generally necessary for TDM, although the laboratory should be called to confirm special handling procedures. Serum separator tubes should, however, be avoided. Serum separator tubes contain silicon, which may bind anticonvulsant drugs. Either these tubes should not be used or serum should be withdrawn from the tube immediately after centrifugation (Boothe, 1998).

Interpretation of TDM results can be facilitated by a clinical pharmacologist. We use the algorithms noted in Figures 24–4 and 24–5 to facilitate interpretation and to make recommendations. Therapeutic failure should not be considered if a patient is seizuring simply because the therapeutic range has been achieved. The hazards of using a therapeutic range as a guide to clinical response are discussed in Chapter 1. Monitoring should be used to identify the therapeutic range for the individual patient. Thus, for a patient that is not sufficiently controlled, doses can be increased gradually until the maximum range has been reached and the risk of adverse affects becomes too great. For patients who react adversely to the drug at concentrations below the maximum therapeutic range, TDM can be used to establish the maximum that can be targeted in such patients. Alternatively, many patients require and can tolerate concentrations of less toxic drugs (e.g., bromide) despite concentrations well above the maximum recommended. Again, TDM is used to establish the range for these patients.

We use a "stair-step" approach to dose modification as delineated in the algorithms. For example, we increase phenobarbital by 5 μg/mL in patients that have not sufficiently responded. Generally, this requires an approximate increase in dose by 25%. After steady-state concentrations have been reached plus one seizure interval, the patient is reassessed. The incremental increase is continued until



Target serum bromide
1.0–3.0 mg/mL

‡No — Is patient seizuring? — Yes†‡||¶

<0.5
If patient is seizure free >6 months and history is supportive, consider discontinuing drug slowly over 3–4 months

0.5–1.0
Load with 225 mg/kg and/or increase maintenance dose by 25%–50%

>1.0–2.5
Maintain dose. Check monthly until steady state; then check every 6 months

>1.5–3.0
If no signs of toxicity, as above; if toxicosis, as below

>3.0
If signs of toxicosis, decrease dose 25% per month to minimum effective dose. Note clinical response may not be evident for 1–2 weeks

* This algorithm can be used regardless of other anticonvulsant drugs. Anticipate lower concentrations to be necessary or risk of toxicity increased with combination therapy.

† Loading doses are recommended for patients with severe seizure history requiring rapid control.

‡ Number in box refers to patient's current serum bromide level (mg/mL).

§ Patient should be at steady state or a loading dose was implemented for this algorithm to be useful. Steady state concentrations require approximately 3 months of administration at the same dose. Any change in the dosing regimen (or patient's health) will require another 3–4 months for a new steady state to be reached.

|| Any dose increase is likely to cause an increase in grogginess. The grogginess should resolve within 1–2 weeks. Grogginess may not be evident, however, until a new steady state is reached.

¶ Bromide concentrations should be checked within several days of completing a loading dose and 1 month later. If 1 month concentrations do not equal post-load concentrations, the maintenance dose should be changed proportionally to the desired change in serum drug concentration. For example, a 25% increase in serum bromide will require a 25% increase in the maintenance dose.

<1.0
Load with 225–400 mg/kg and increase maintenance dose 25%–50%, targeting 1.0 mg/mL. Recheck after loading and at 1 and 6 months

1.0 to <1.5
Load with 150–300 mg/kg and increase maintenance dose 25%–50%, targeting 1.5–1.75 mg/mL. Recheck after loading and at 1 and 6 months

1.5 to <2.0
Load with 225–350 mg/kg and increase maintenance dose by 25%–50%, targeting 2.0–2.25 mg/mL. Check after loading and at 1 and 6 months

2.0 to <2.5
Load with 300–400 mg/kg, increase dose 25%–50%, targeting 2.5–2.75 mg/mL. Check as above

>2.5 to <3
As above, targeting 3.0–3.25. Watch closely for bromide toxicity

>3.0 to <3.5
As above, targeting 3.5–3.75

Figure 24–5. Algorithm for dose modification for bromide dosing regimens.

minutes. Failure to control seizures may indicate the need for pentobarbital, which is a general anesthetic, not an anticonvulsant. As such, the risk of cardiovascular or respiratory depression is great. An advantage to the use of pentobarbital, however, is its protective effects on the brain during periods of hypoxia induced by the seizure.

Alternative routes of anticonvulsant therapy might be considered for clients attempting to control life-threatening seizures without immediate access to veterinary medical assistance. Phenobarbital (5 mg/kg), diazepam, and lorazepam are partially bioavailable after rectal administration (Mealey and Boothe, 1995; Papich and Alcorn, 1995). Bromide also can be given rectally. The risk of potassium overload can be minimized by administration of the loading dose over a 12- to 24-hour period in 5- to 15-mL increments.

General gas anesthesia generally should be avoided in the patient with status epilepticus because of the risk of hepatotoxicity induced by the anesthetic that may occur with prolonged therapy. If pursued, anesthetics that are minimally hepatotoxic should be selected. Discontinuation of therapy should be undertaken cautiously to minimize the risk of seizures. Propofol and etomidate are two chemical restraining agents that, although expensive, are characterized by anticonvulsant effects. Of the two, etomidate (a human drug only) may be characterized by CNS protective effects. These drugs can be administered as IV infusions to effect (see later discussion under brain trauma).

Status epilepticus may require management of cerebral edema (see later discussion of brain trauma and injury).

Chronic Control

What constitutes successful anticonvulsant therapy will vary among clinicians and may be defined as client satisfaction. Eradication of seizures may be an unachievable goal; decreased frequency, severity, or duration of the seizure episode may be considered a success for many animals. Indeed, close counseling of clients and reorientation to what constitutes successful control may be important techniques to successfully treating an epileptic dog.

If manipulation of a dosing regimen is the focus of successful control, a chosen therapeutic regimen should not be abandoned until steady-state plasma drug concentrations have been reached. Thus, an animal should not be considered refractory to a drug simply because it is receiving more than the recommended dose or its serum concentrations are within the therapeutic range. A drug should not be abandoned until serum concentrations in the maximum therapeutic range (or, for bromide, potentially well exceeded) have been documented or unacceptable adverse side effects occur. Regardless of the anticonvulsant used, therapy should never be stopped suddenly, and drug concentrations should not be allowed to drop precipitously during a dosing interval. Status epilepticus may occur.

Anticonvulsant-induced liver disease should be distinguished from hepatic induction induced by either phenobarbital or primidone. Phenobarbital and primidone administered chronically cause nonpathologic changes in the livers of most patients. Moderate elevations in the serum transaminases and serum alkaline phosphatase activity and abnormalities (more than 50 mol/L) in fasting bile acids and serum albumin are indicative of hepatic pathology. The incidence of serious liver toxicity can be reduced by avoiding combination therapy with more than one drug metabolized by the liver, using TDM (Neff-Davis, 1988) (see Chapter 4) to achieve adequate serum concentrations at the smallest dose possible, and evaluating hepatic function every 6 months or more, depending on the magnitude of phenobarbital serum concentrations. The higher the plasma drug concentration, the more important hepatic monitoring becomes. Seizure-induced hypoxia can result in liver damage; thus, evaluation of the liver should not occur in association with a seizure episode. Hepatotoxicity induced by anticonvulsants is often reversible if the drug dose is sufficiently decreased before cirrhotic changes occur.

Phenobarbital has remained the first-choice anticonvulsant for chronic control of seizures in both dogs and cats due to its efficacy and, as long as drug concentrations do not approach the maximum therapeutic concentration, safety. Therapeutic drug monitoring should be used to ensure that adequate serum drug concentrations have been achieved before the patient is considered refractory. As concentrations of phenobarbital approach the maximum end of the therapeutic range, an alternative regimen should be considered. The addition of a second anticonvulsant is the most likely next step.

Bromide is recommended as the first combination drug of choice for dogs should phenobarbital therapy fail. Bromide increasingly is being used as the sole anticonvulsant, although a severe seizure history may warrant using a more accepted and predictable first-choice drug (i.e., phenobarbital). Controlling refractory seizures with bromide has been facilitated in our laboratory using a stair-step approach. We increase bromide concentrations in 0.5-mg/mL increments (see Fig. 24–5). If the patient develops seizures at one concentration, the concentration is increased to the next level. This is continued until the patient is acceptably controlled or sedation becomes untenable. In the latter case, decreasing phenobarbital concentrations by 25% may help resolve grogginess. If the goal of bromide therapy is to wean the patient off phenobarbital, we confirm that bromide concentrations are at least 1.5 mg/mL and decrease phenobarbital by 25% each 2 to 4 weeks. We monitor phenobarbital at each decrease in dosage so that we have a target should seizures return. Some animals require bromide concentrations of 2.5 mg/mL or higher before phenobarbital can be lowered to less than 20 μg/mL (our standard goal). Phenobarbital may not be "decreasable" in some patients, despite bromide concentrations that approach 3 mg/mL. On the other hand, some patients can be totally "weaned" off phenobarbital.

Diazepam has been the second drug of choice for chronic control of seizures in cats. Bromide as either the sodium or potassium salt also has been useful in cats. However, bronchial asthma may be an undesirable complication. For patients for whom bromide and phenobarbital cannot control seizures (after maximum therapeutic concentrations of both drugs have been documented) or for patients that are unacceptably groggy, a third anticonvulsant can be added. The third drug should be anticipated to provide better control or allow a decrease in one of the anticonvulsants (preferably phenobarbital) to minimize grogginess. Felbamate and clorazepate have been used by the author in this capacity. Fine tuning of the proper doses should be accompanied by monitoring whenever possible.

Drugs Contraindicated for Epileptic Patients

Reserpine, phenothiazine, and butyrophenone tranquilizers are contraindicated for epileptic patients because they can induce seizures. Other drugs capable of inducing seizures in selected patients include fluorinated quinolones, lidocaine, and possibly metoclopramide. Seizures induced by lidocaine should be treated with a benzodiazepine (e.g., diazepam) (Sawaki et al., 2000). Morphine sulfate and related compounds as well as CNS stimulants such as the methylxanthines and behavior-modifying drugs should be avoided. Chloramphenicol also activates the CNS and should not be used in dogs known to have epileptiform seizures. Glucocorticoids may also decrease seizure threshold, although they stabilize neuronal membranes. Long-term effects on the neuronal membrane, however, may reflect down-regulation of glucocorticoid receptors and thus loss of the stabilizing effect. Long-term use of glucocorticoids might be minimized for epileptic patients. In general, drugs for which CNS derangements or seizures are a listed side effect should be avoided in epileptic animals.

ANTICONVULSANT DRUGS

Phenobarbital

Mechanism of Action

Phenobarbital sodium (see Fig. 24–2) specifically depresses the motor centers of the cerebral cortex, thus enhancing anticonvulsant properties. Electroshock experiments with cats and other species established phenobarbital as one of the most potent anticonvulsants available. It has the widest spectrum of activity in different convulsive seizure patterns. Most other antiepileptic agents have been synthesized as structural variants of phenobarbital (de Angelis, 1979). For example, primidone is a close congener of phenobarbital.

Phenobarbital is the most effective anticonvulsant to delay progressive intensification of seizure activity that may accompany epilepsy. Phenobarbital both increases the seizure threshold required for seizure discharge and decreases the spread of discharge to surrounding neurons. The primary means by which phenobarbital decreases seizure activity is by enhancing responsiveness to the inhibitory postsynaptic effects of GABA. Interaction of GABA opens a chloride channel, resulting in higher intracellular concen-

months for its complete disappearance in the dog. In newborn rats, phenobarbital induces a long-term, perhaps permanent, alteration in hepatic mixed-function oxidase activity (Faris and Campbell, 1981). Induction can alter the elimination half-life and thus duration of therapeutic response to other drugs metabolized by the liver. Many drugs have been shown to be affected, including among others in the dog, digoxin and digitoxin (Ravis et al., 1987; Breznock, 1975) and thiopental (Sams and Muir, 1988). Because induction increases the production of potentially toxic metabolites, potentially hepatotoxic drugs should not be used with phenobarbital. *N*-acetylcysteine might be used in cases of acute hepatopathy.

Side Effects

Behavior. Polyphagia, polydipsia, and polyuria are side effects that occur in animals receiving clinical dosages of phenobarbital (Kay and Fenner, 1977). The polyuric effect is apparently due to an inhibitory action in the release of antidiuretic hormone. Identical sedative side effects are observed in the dog after treatment with phenobarbital or primidone (Schwartz-Porsche et al., 1985). Dogs appear fatigued and listless after receiving either drug; some are weak in the rear legs, and ataxia occurs. All of these effects may be long lasting and may persist in some cases for the duration of treatment; however, tolerance to these effects will develop in many dogs within 1 to 2 weeks after initiating the dosing regimens.

Bone Marrow Dyscrasias. Phenobarbital can cause what is an apparent allergic reaction manifested as a bone marrow dyscrasia in dogs. Pancytopenia or (more commonly) neutropenia is detected after a complete blood count in animals that presented with a variety of clinical signs. Bone marrow suppression generally resolves rapidly once phenobarbital is discontinued. Care should be taken to begin an alternative anticonvulsant drug (e.g., bromide) in animals that are at risk for worsening of seizures should phenobarbital be rapidly discontinued. Phenobarbital-induced coagulation has been reported in the cat (Solomon et al., 1974).

Thyroid. Phenobarbital can induce tissue (peripheral tissues and the liver) metabolism of thyroid hormones. Thyroxine (free and total) decreased in one study (Muller et al., 2000a) and TSH response was delayed. Apparently, thyroid-stimulating hormone can be similarly affected. Thyroid screens in apparently normal animals that yield results indicative of hypothyroidism do not necessarily indicate the need for treatment. On the other hand, if an animal presents with clinical signs consistent with hypothyroidism, replacement therapy may be indicated.

Hepatotoxicity. At high plasma drug concentrations (i.e., more than 30 to 40 μg/mL), phenobarbital appears to be hepatotoxic. Animals whose liver is induced and thus require high doses of phenobarbital to maintain drug concentrations in the lower therapeutic range may also be more susceptible to toxicity because of increased formation of metabolites. Phenobarbital will also cause nonpathologic changes in hepatic clinical laboratory tests due to induction of enzymes. Serum alkaline phosphatase (SAP) and the transaminases are likely to increase with chronic therapy (Muller et al., 2000b; Bunch et al., 1984, 1987; Bunch, 1993; Dayrell-Hart et al., 1991). These are not necessarily indicative of liver disease. Changes associated with true hepatic pathology are more likely with primidone (see later). Moderate elevations in alanine transaminase and SAP, coupled with changes in bile acids, are more indicative of hepatic pathology (i.e., liver disease). Hepatic function tests (e.g., serum bile acids) should be studied to monitor the development and/or progression of liver disease. Bilirubin has not been a sensitive indicator of liver disease induced by phenobarbital for the author; indeed, it generally increases only with end stage liver disease, if at all. Interestingly, decreased serum cholesterol levels have occurred relatively early. Decreased serum urea nitrogen and albumin levels are supportive of phenobarbital-induced hepatic disease and the need for rapid but cautious withdrawal of phenobarbital in concert with initiation of an alternative anticonvulsant. The incidence of serious liver toxicity can be reduced by avoiding combination therapy, using TDM to achieve adequate serum concentrations at the smallest dose possible, and evaluating clinical pathology changes every 4 to 6 months while the patient is receiving therapy. Note that liver enzymes are generally increased after a seizure due to the effects of, for example, hypoxia. Hepatotoxicity at lower concentrations is much less common.

Treatment of Acute Phenobarbital Toxicosis

Treatment of acute phenobarbital toxicosis is generally supportive. Dogs apparently can tolerate marked overdosing (concentrations approximately 150 μg/mL) without persistent effects once sedation has resolved. Artificial respiration with oxygen should be administered to prevent hypoxia from respiratory arrest induced by overdoses of phenobarbital. Although less effective than oxygen, doxapram or other analeptic drugs may be used to stimulate the respiratory center. Also, alkalinization of the urine accelerates renal excretion of phenobarbital; increased ionization of phenobarbital by this alkalinization hastens elimination of the drug (de Angelis, 1979). Activated charcoal effectively accelerates the body clearance of phenobarbital (Berg et al., 1982). When charcoal is administered in the human, the biologic half-life of phenobarbital is decreased from 110 ± 8 to 45 ± 6 hours; it increases the total body clearance of phenobarbital from 4.4 ± 0.2 to 12.0 ± 1.6 mL/kg per hour (Berg et al., 1982). *N*-acetylcysteine might also be administered as for acetaminophen toxicosis.

Primidone

Primidone is metabolized in the liver to phenylethylmalonic acid (PEMA) and phenobarbital (Frey et al., 1979) (see Fig. 24–3). Although all three compounds have anticonvulsant activities, phenobarbital is much more potent and has a longer half-life than primidone and PEMA (and thus accumulates). Phenobarbital concentrations can be correlated with primidone efficacy and should be monitored rather than primidone. The side effects noted for phenobarbital occur with primidone as well. Target therapeutic ranges are the same as for phenobarbital. Primidone continues to be used for patients that have proved refractory to phenobarbital at the maximum therapeutic drug concentration (i.e., 40 μg/mL). Note that its efficacy in this scenario has not been proved (Porsche et al., 1985; Schwartz-Porsche et al., 1982). Efficacy may simply reflect improved conversion to phenobarbital (i.e., animals that are induced may metabolize the drug to greater concentrations of phenobarbital than generated from administration of phenobarbital alone). According to Farnbach (1984a), there is no advantage to using primidone rather than phenobarbital for control of epilepsy in most dogs.

The conversion ratio of primidone to phenobarbital is 3.8:1. A patient should receive approximately 65 mg (1 grain) of phenobarbital for each 250 mg primidone. Because this rate does not reflect the potential effects of phenobarbital (i.e., primidone) induction, however, animals may convert primidone to phenobarbital at different rates. Baseline phenobarbital concentrations should be established prior to conversion. Conversion should probably be progressive (e.g., 25% change each month) in patients whose seizure history includes prolonged or cluster seizures. Cats do not metabolize primidone to phenobarbital as efficiently as dogs (Sawchuk et al., 1985). Although primidone is reportedly safe in cats, the study on which this report is based did not include administration of primidone in doses sufficient to generate therapeutic concentrations of phenobarbital. Thus, the safety of primidone at effective concentrations has not been established in cats, and we do not recommend its use for the treatment of feline seizures.

Side Effects

The sedative side effects of primidone in the dog are the same as those with phenobarbital (Schwartz-Porsche et al., 1985; see earlier discussion of the antiepileptic action of phenobarbital). In fact, primidone causes all of the side effects noted for phenobarbital. Primidone may induce nystagmus, nausea, drowsiness, and ataxia. According to Schwartz-Porsche et al. (1985), polydipsia is more common in dogs treated with primidone. In humans, it is recommended that therapeutic plasma concentrations of primidone and its metabolite phenobarbital not exceed 15 and 30 μg/mL, respectively. Megaloblastic anemia is one of the more serious adverse effects of primidone in humans.

In the dog, primidone induces progressive hepatic injury as manifested by increases in liver enzyme values (Meyer and Noonan, 1981). In a clinical study, signs of liver toxicity were reported in 14 of 20 dogs (Schwartz-Porsche et al., 1985). Hepatic cirrhosis associated with primidone and phenobarbital after 7 years of use has been reported in a dog (Poffenbarger and Hardy, 1985). Dermatitis has been reported in the dog (Hendricks, 1987).

In humans, long-term (more than 2 years) treatment of epileptic patients with primidone has been associated with development of osteomalacia; subnormal serum calcium is seen in such patients. Primidone may induce or stimulate increased production of hepatic microsomal enzymes that increase the metabolism or degradation of vitamin D.

Drug Interactions

Drug interactions previously described for phenobarbital also occur with primidone. Primidone should not be used concurrently with chloramphenicol, which is a potent inhibitor of the microsomal enzyme system. Severe CNS depression and inappetence occur in the dog after concurrent use of these drugs (Campbell, 1983).

Phenytoin Sodium

Phenytoin sodium, previously named diphenylhydantoin, depresses motor areas of the cortex (antiepileptic action) without depressing sensory areas. It is approved by the U.S. Food and Drug Administration (FDA) for control of epileptiform convulsions in dogs.

Phenytoin is a hydantoin derivative (see Fig. 24–2) (de Angelis, 1979); others of lesser importance are mephenytoin and ethotoin. Hydantoins are five-membered ring structures, whereas barbiturates are six-membered structures. A major point of difference between the hydantoins and barbiturates is the absence of a C=O group. Phenytoin is not a general anticonvulsant, as is phenobarbital, and is not used for emergency treatment of poisoning by convulsant drugs or tetanic seizures. Oral preparations are available in suspension, capsule, and tablet forms. Phenytoin (50 mg/mL) is also available for human use in a special solvent for IV administration. Intravenous injection of the drug causes a marked drop in arterial pressure and is not advised in the dog (Pasten, 1977).

Use of phenytoin to control seizures in the dog has declined because of its lack of efficacy (Sanders and Yeary, 1978), which may be related to decreased bioavailability and rapid clearance. Phenytoin is much less effective in the dog than either phenobarbital or primidone in the control of epileptic seizures (Farnbach, 1984a). The half-life of phenytoin is too short in the dog to permit maintenance of adequate drug concentrations in plasma and the CNS (Schwartz-Porsche et al., 1985). When administered alone, phenytoin cannot be considered a satisfactory drug for treatment of epilepsy in the dog (Frey and Loscher, 1980; Frey, 1986). Due to drug interactions and enhanced hepatotoxicity, a combination of phenytoin with phenobarbital is not a viable alternative.

In the cat, phenytoin is relatively toxic and generally undesirable as an anticonvulsant (Kay and Fenner, 1977). Studies are needed to determine the efficacy and safety of phenytoin for cats (Frey, 1986).

Pharmacologic Activity

Phenytoin produces a stabilizing effect on synaptic junctions that ordinarily allow nerve impulses to be readily transmitted at lower thresholds. Consequently, the level of synaptic excitability that permits impulses to be transmitted easily is reduced or stabilized or both. This effect appears to be associated with active extrusion of Na^+ from neurons and decreased post-tetanic potentiation or spread of nerve impulses to adjacent neurons. There is also a possibility that phenytoin reduces movement of calcium across cell membranes. Phenytoin may inhibit activation of protein phosphorylation by the calcium/calmodulin complex (Marx, 1980). Phosphorylation and norepinephrine release in neurons requires calmodulin.

Reduction in spread of the "burst" activity associated with epilepsy prevents genesis of the cortical seizure. The activity of phenytoin in stabilizing hyperexcitable neurons so that epileptic seizure does not develop occurs without causing general depression of the CNS (de Angelis, 1979).

Disposition

Absorption of phenytoin is erratic following intramuscular (IM) administration. This may be related to crystallization of the drug at the injection site because of alteration in pH by tissues (de Angelis, 1979). Administration of phenytoin by the IM route is not advised because considerable necrosis and sloughing at the injection site occur (Pasten, 1977). Absorption of the drug from the GI tract of the dog is poor (Sanders and Yeary, 1978). Bioavailability of phenytoin from the tablet formulation averages 36% in the dog (Frey and Loscher, 1980). Poor oral absorption and differences in product bioavailability contribute to the difficulty in achieving effective serum levels of phenytoin. The generic preparations of phenytoin should not be used.

At therapeutic concentrations (10 to 20 μg/mL), phenytoin is highly bound (75% to 85%) to plasma proteins in animals and humans (Baggot and Davis, 1973). The high degree of phenytoin binding predisposes this acidic drug to interaction with other drugs by a displacing effect at protein (albumin) binding sites. In uremic patients, there is a decrease in plasma protein binding of phenytoin. This accelerates renal clearance or elimination of the drug. Phenytoin readily crosses the placenta (Mirkin, 1975). High concentrations are attained in the maternal liver and maternal and fetal hearts. The brain (ostensibly the primary target organ) contains nearly the lowest concentration of the drug.

Phenytoin is metabolized into metahydroxyphenytoin or parahydroxyphenytoin. These metabolites are then conjugated with glucuronic acid. In humans, about 60% to 75% of the daily dose of phenytoin is excreted in the glucuronide form (de Angelis, 1979); the dog also converts a high percentage of phenytoin into this form. In addition, diphenylhydantoic acid, a minor metabolite in some laboratory animals, and dihydrodiol are formed. Interestingly, high concentrations of diphenylhydantoic acid are found in cat urine. The dihydrodiol metabolite is probably involved in formation of catechol metabolites; these are also formed in most animals (Glazko, 1973). Epoxide metabolites are also speculated to be formed in humans. The combined use of phenytoin and phenobarbital or primidone may lead to increased formation of epoxide metabolites in animals. This could possibly result in cholestatic hepatic injury similar to that reported in three dogs (Bunch et al., 1987). Because phenytoin is not very soluble in water, little of the unmetabolized drug is excreted in urine.

Phenytoin has a long duration of action in the cat. Due to the long plasma half-life (about 24 to 108 hours) (Tobin et al., 1973), the prolonged effect of phenytoin observed in the cat more than in other species may also be related to its decreased ability to conjugate compounds with glucuronic acid. Phenytoin is excreted after formation of a hydroxylated derivative and conjugation with glucuronic acid or sulfate. A plasma half-life of 108 hours after oral administration of phenytoin (10 mg/kg) in the cat has been reported (Roye et al., 1973). In the dog, despite relatively large single daily doses (50 mg/kg) administered orally, the plasma concentration of the drug is low. Paralleling this observation, the plasma half-life of a single 50 mg/kg dose in the dog is only 6 to 7.8 hours (Dayton et al., 1967). Roye et al. (1973) found that the plasma half-life was 4 to 6 hours after an IM injection of phenytoin (50 mg/kg). The apparent discrepancy between the results of these two studies may be due to pretreatment of the dogs for 9 days with phenytoin by Roye et al. (1973). Induction of hepatic microsomal enzyme activity may have accounted for the shorter plasma half-life. Studies have shown that the half-life of phenytoin in the dog dramatically decreases after 7 to 9 days of treatment (Frey and Loscher, 1980). Apparently, phenytoin is a potent inducer of the hepatic microsomal enzyme system in the dog. Other biologic half-life data reported in the dog are as follows: After a single IV dose (15 mg/kg), a value of 4.5 hours was obtained by Sanders et al. (1979b), and a half-life of 3.65 hours was determined by Pedersoli et al. (1981) after an IV bolus of 11 mg/kg.

Clinical Use

Recommended therapeutic doses of phenytoin administered orally every 8 hours for control of seizure disorders in the dog indicate considerable variation: 6.6 to 11 mg/kg (Pasten, 1977); 11 mg/kg (Cunningham, 1984); and 35 mg/kg (Sanders and Yary, 1978). In humans, clinical therapeutic effects and intoxication are related to the blood concentration of phenytoin. A reduction in the number of seizures occurs when phenytoin blood concentrations exceed 10 μg/mL.

Because the half-life of phenytoin in the dog is reduced considerably after use for 7 to 9 days (Frey and Loscher, 1980), high oral doses up to 30 mg/kg every 8 hours may be required for satisfactory control of seizures (Cunningham, 1984). Oral administration of phenytoin (4.4 and 11 mg/kg) every 8 hours fails to reach the so-called therapeutic level of the drug in serum at 10 μg/mL. The serum content of phenytoin in the dog after single or repeated oral doses of 10 mg/kg does not exceed a concentration of 2 μg/mL (Sanders and Yeary, 1978). To achieve a serum concentration of approximately 10 μg/mL phenytoin, it appears that an oral dose of at least 35 mg/kg given three times daily is necessary for the adult dog (Sanders and Yeary, 1978). According to Pedersoli et al. (1981), an oral dosage schedule of 20 mg/kg every 8 hours of the phenytoin microcrystalline suspension should be sufficient to reach a serum concentration of 10 μg/mL or higher. This dose, however, will only maintain a plasma therapeutic level for the first 2 or 3 days of treatment (Frey and Loscher, 1980). The marked variation in the dosage of phenytoin needed to maintain a therapeutic level in the dog is attributable in large measure to its rapid biotransformation by the hepatic microsomal enzyme system.

Drug Interactions

Phenytoin must be considered a potent inducer of the hepatic microsomal enzyme system in the dog (Frey and Loscher, 1980). Seven to 9 days after administration of phenytoin, its half-life may be reduced from 5.5 to 1.3 hours. In contrast, the half-life after oral administration in humans averages 22 hours, with a range of 7 to 42 hours.

Phenytoin has moderate ability in the human to induce cytochrome P-450 mixed-function oxidase activity (microsomal enzyme induction). Consequently, it is a much more efficacious drug for control of epileptic seizures in humans than in dogs. Phenytoin and phenobarbital have been used in combination for treatment of epilepsy in both humans and dogs. This combined use is considered optimal therapy for epilepsy in humans (Morselli et al., 1971). Use of both drugs is controversial because both drugs induce hepatic microsomal enzyme activity. The metabolism (i.e., hydroxylation) of phenytoin is increased. Phenytoin likewise increases the metabolism of phenobarbital. This see-saw effect in the metabolism of both drugs complicates successful therapy, and the combined use of the drugs is discouraged (Pasten, 1977).

Inhibition of phenytoin metabolism by other drugs has been observed in humans. Prolongation of the effect has been reported after simultaneous administration of dicumarol, chloramphenicol, phenylbutazone, and the phenothiazines. Also, in vitro inhibition of phenytoin metabolism has been seen in the presence of diazepam and propoxyphene hydrochloride. The significance of this in vivo has not been determined. Metabolism of a number of chemicals or drugs is enhanced by phenytoin. These include digitoxin, dexamethasone, dichlorodiphenyltrichloroethane, dieldrin, and cortisol (Conney and Burns, 1972). In the dog, an interaction has been seen after clinical use of phenytoin and chloramphenicol (Sanders et al., 1979a). The serum half-life of IV phenytoin is increased from 3 to 15 hours. The increase in the serum half-life is best explained by a reduction in the rate of metabolism of phenytoin by hepatic microsomal enzymes. Interestingly, the signs of phenytoin toxicosis are reversed within 24 hours after cessation of chloramphenicol treatment (Sanders et al., 1979a). Phenylbutazone is also known to elevate plasma concentration of phenytoin through inhibition of metabolism of phenytoin (de Angelis, 1979).

An interaction also exists between phenytoin and vitamin B_6. Serum phenytoin concentration may drop after folic acid therapy ostensibly because the hydroxylase enzyme metabolizing phenytoin is folate dependent. In humans, the usual therapeutic concentration of phenytoin in plasma reduces the half-life of theophylline (a drug used in the treatment of airway obstruction) and increases its body clearance about twofold (Marquis et al., 1982). A similar action of phenytoin on the half-life of theophylline in animals would be expected.

Phenytoin may prolong the prothrombin time (Keith et al., 1983). Blood coagulation defects similar to that induced by vitamin K deficiency can occur in neonates exposed to phenytoin in utero. The coagulation defect can be reversed by treatment with vitamin K.

Blood Concentrations and Associated Toxicity

In humans, mild signs of intoxication such as nystagmus develop with blood levels of 20 μg/mL; patients with levels over 40 μg/mL have marked nystagmus and are incoordinated and lethargic. Blood levels in the dog would probably have to increase a comparable 100% to 400% as in humans before serious signs of intoxication develop.

Hepatitis, jaundice, and death after clinical use of phenytoin have been reported (Nash et al., 1977). In that case, however, the animal had initially received primidone (500 mg daily) orally for the control of seizures. Toxic hepatopathy and intrahepatic cholestasis associated with phenytoin administration in combination with phenobarbital and/or primidone have been reported in three dogs (Meyer and Noonan, 1981; Bunch et al., 1987). Induction of enzymes may increase the formation of toxic metabolites, which may contribute to hepatotoxicity. Hepatotoxicity due to phenytoin is more likely if used in combination therapy with either primidone or phenobarbital. Toxicity may be related to generation of toxic metabolites. Two forms of toxicity appear to occur with phenytoin therapy: a dose-independent chronic hepatitis that may progress to cirrhosis and that appears to be reversible after discontinuation of the drug early in the disease; and a dose-dependent intrahepatic cholestasis that is accompanied by a poor prognosis.

Other Side Effects

The side effects of phenytoin in the dog are moderate because it is rapidly metabolized (Cunningham, 1984). Transient incoordination and oversedation may occasionally occur after administration of phenytoin. A moderate degree of polyphagia, polydipsia, and polyuria may be seen in animals medicated with this drug. Sialosis, weight loss, and vomiting have been reported after the use of phenytoin in the cat. Inhibition of release of antidiuretic hormone accounts for the polyuria that develops after administration of phenytoin. There is also an inhibition of insulin secretion (de Angelis, 1979).

Benzodiazepines: Diazepam, Clorazepate, Clonazepam, and Lorazepam

Mechanism of Action

Benzodiazepines enhance the inhibitory effects of GABA in both the brain and spinal cord (see Fig. 24–3). Thus they not only decrease seizure spread but also block arousal and centrally depress spinal reflexes (see Chapter 26). Tolerance to the anticonvulsant activity of diazepam develops rapidly, within 1 week, in the dog; thus, diazepam is not an effective anticonvulsant for chronic therapy in dogs. Intravenous diazepam is, however, the drug of choice for the treatment of status epilepticus in both dogs and cats because it crosses the blood-brain barrier into the cerebrospinal fluid very rapidly. Diazepam (1 to 2 mg every 8 hours) is also the second choice anticonvulsant for chronic control of seizures in the cat whose seizures do not respond to phenobarbital; efficacy is equal to phenobarbital. Tolerance to the anticonvulsant effects of clorazepate does not appear to develop in dogs as easily as it does to diazepam, although abrupt seizures may occur with rapid withdrawal.

Disposition

Diazepam is the prototype benzodiazepine used in small animals. The drug is well absorbed after oral administration but undergoes rapid and extensive hepatic metabolism once

although bioavailability in pediatric animals may be as little as 30% of that in adult dogs, necessitating a higher dose (Yang et al., 1992). The drug is eliminated by hepatic metabolism to metabolites that are largely inactive (Yang et al., 1992). In adult dogs, the half-life of felbamate is 4 to 8 hours (mean of 5.2 hours); the elimination half-life is shorter in pediatric (beagle) dogs (mean of 2.5 hours) (Adusumalli et al., 1992). Safety has been documented at doses ranging from 15 mg/kg divided twice daily (the starting therapeutic dose) to 300 mg/kg. Peak felbamate concentrations following oral administration of 60 mg/kg in dogs was 12.6 to 168 μg/mL.

Sedation, polyuria, polyphagia, and polydipsia, side effects typical of most anticonvulsants, do not appear to occur in dogs. Aplastic anemia due to bone marrow suppression, however, developed in 10 of 100,000 patients (human) receiving felbamate (Theodore, 1997). We have not experienced any type of bone marrow suppression in dogs receiving felbamate. Although the drug has not been withdrawn, it is now much harder to acquire, and it is not likely to become less expensive. We have seen no toxicities with this drug, including hepatotoxicity. Because felbamate is a drug metabolized by the liver, however, prudence suggests that combination with phenobarbital, particularly in patients requiring high serum concentrations of phenobarbital to control seizures, be avoided. Currently, there is no easy, cost-effective means for assaying felbamate, although selected laboratories offer the service. The drug does appear to be sufficiently safe that monitoring may not be necessary. Human therapeutic concentrations range from 20 to 100 mg/L, with trough concentrations ideally remaining in the range of 60 to 80 mg/L for best efficacy (Graves, 1993). The clinical use of felbamate is currently being studied in dogs. If seizures are not controlled with the starting dose (15 mg/kg divided every 12 hours), we progressively increase the dose in 15 mg/kg increments. We have administered felbamate to dogs at doses as high as 300 mg/kg divided daily for over 6 months with no apparent adverse effects. Phenobarbital concentrations should be monitored as the dose of felbamate is increased because drug interactions can complicate therapy. In humans, interactions have lead to increases in phenobarbital by felbamate (Reidenberg et al., 1995), although this appears to be due to selective inhibition of a cytochrome P450 enzyme in only 25% of the population. We have not seen an increase in phenobarbital concentrations, and caution is indicated in decreasing phenobarbital doses in anticipation of drug interactions. Greater risk may reflect decreased felbamate concentrations due to induction by phenobarbital (Reidenberg et al., 1995). Phenobarbital concentrations might be reduced in patients whose seizures are controlled with felbamate. We do not decrease phenobarbital concentrations below baseline values, however, until seizures have been controlled for at least two seizure intervals. Complete blood counts ideally should be performed at 2- to 3-month intervals and the liver should be monitored as for phenobarbital.

Gabapentin

Gabapentin is an anticonvulsant approved in 1994 for treatment of partial seizures with or without generalization in humans with epilepsy (Goa and Sorkin, 1993; McLean, 1994; Ramsey, 1994). It appears to act by a novel mechanism by promoting the release of GABA, although the actual mechanism of release is not known. Although gabapentin is absorbed well after oral administration, its absorption appears to be dose dependent, relying on a saturable transport process. This process has been cited as the reason that antiepileptic effects last longer than anticipated based on drug half-life, allowing twice daily administration. In contrast to bromide, the short half-life of gabapentin (in humans) results in steady-state concentrations within 24 to 48 hours. The drug is eliminated in people entirely by renal elimination, thus avoiding some of the risks of hepatotoxicity and drug interaction. The drug is sufficiently safe that TDM is not necessary; rather, the dose is increased as needed to control seizures. Mild dizziness, nausea, and vomiting have occurred in a small percentage of human patients.

Gabapentin studies with animals have not been reported. One of the major disadvantages of this drug is its expense. Unfortunately, the manufacturers are not willing to provide the drug for the study, and the expense of a controlled clinical trial with dogs may preclude its clinical study. Despite its expense, our experience has been that some clients will pay the cost to use gabapentin (up to $85/month for a 30-kg dog dosed at 10 to 30 mg/kg orally every 8 hours; 60 mg/kg every 8 hours has also been recommended). Unfortunately, even if combined with phenobarbital, gabapentin does not appear to be effective for the control of epilepsy when used at doses extrapolated from human patients. Response may be more likely at higher doses, but cost becomes prohibitively more expensive. Thus, the role of gabapentin in the treatment of epilepsy in dogs is uncertain.

Valproic Acid

Valproic acid is a vehicle used for other drugs that was serendipitously found to have anticonvulsant properties. It is a simple branched-chain carboxylic acid (see Fig. 24–2). Valproic acid is effective against a variety of seizures, including absence seizures. Its mechanism of action appears to be similar to that of phenytoin in that it prolongs recovery of voltage-activated Na^+ channels from inactivation. It may also affect Ca^{2+} fluxes but does not appear to impair GABA. The drug is rapidly absorbed, highly protein bound, and in humans has a half-life of 10 to 15 hours. The half-life can, however, be shortened in the presence of other (inducing) anticonvulsant drugs.

The difficulty in using this drug in dogs probably reflects an inability to achieve therapeutic concentrations. Valproic acid is metabolized in the liver; metabolites can be as potent as the parent compound in controlling seizures, although only one of them enters the CNS to any appreciable extent. Valproic acid can alter liver enzymes (up to 40% of human); increases can be associated with toxicity. Hepatotoxicity is likely to be increased when used in combination with other drugs. It also causes gastrointestinal upset and, like other anticonvulsants, CNS side effects (e.g., sedation, ataxia). Valproic acid has not proved very useful for controlling seizures in dogs. It might be considered in combination with phenobarbital, although drug interactions may complicate therapy.

Mephenytoin

Mephenytoin is a hydantoin derivative, similar to phenytoin. Its anticonvulsant activity results from metabolism to nirvonal, which has a 25-hour half-life in dogs. In humans, this drug has proved very effective for the control of epilepsy. Bone marrow dyscrasias, however, preclude its common use. Unlike phenytoin, mephenytoin is well absorbed after oral administration in dogs, and therapeutic concentrations of nirvonal probably can be achieved. Studies focusing on its use as a sole agent or in combination with phenobarbital have not been done. Although isolated reports suggest that it should prove efficacious (2 mg/kg every 8 hours) in dogs with epilepsy, hepatotoxicity, particularly when combined with phenobarbital, necessitates cautious use.

Pentobarbital Sodium

Pentobarbital sodium (pentobarbitone sodium; Nembutal Sodium), administered intravenously, is considered to be the most efficacious drug for abolishing refractory status epilepticus in the dog (Redding, 1969). Pentobarbital is a general anesthetic (not an anticonvulsant), but it is nonetheless an effective drug for control of nonresponsive seizures; extreme care is required not to overdose. An added advantage of pentobarbital is its ability to scavenge oxygen radicals and decrease cerebral oxygen consumption (see later discussion of increased intracranial pressure). The effective dose varies considerably from one animal to the next. Consequently, pentobarbital is carefully given to effect. Careful monitoring of the cardiovascular and respiratory systems is necessary. Prolonged treatment may be necessary for some patients; some human patients remain anesthetized for up to 9 days before seizures are controlled. For additional information on the pharmacologic and toxicologic effects of pentobarbital, see Chapter 13.

In humans, tonic-clonic status epilepticus, which is refractory to phenobarbital, phenytoin, or diazepam, may respond to an IV infusion of pentobarbital given continuously for 3 days (Young et al., 1983). It is then discontinued, and oral phenobarbital along with other anticonvulsants is advocated to control recurring epileptic episodes.

TREATMENT OF OTHER NEUROLOGIC CONDITIONS

Brain Trauma or Injury

Pathophysiology of Brain Injury

After head trauma, secondary injury occurs in both contused and adjacent tissues (Proulx and Dhupa, 1998). A cascade of events begins with massive depolarization and ion fluxes that initiate increased energy expenditure by the sodium/potassium adenosine triphosphatase (ATPase) pump, the main regulator of cell volume and electrochemical gradient. Systemic hypotension and disrupted cerebral blood flow exacerbate adenosine triphosphate (ATP) depletion. Brain tissue is extremely sensitive to decreased oxygenation. Glutamate, an excitatory NT that allows calcium influx into the neuron, appears to play an important role in the early stages of secondary brain injury caused by head trauma. Normal intracellular concentrations are approximately 1500-fold greater than extracellular concentrations. Well-developed energy-requiring mechanisms exist to maintain very low extracellular glutamate concentrations; this system becomes overwhelmed due to the combined effects of efflux of intracellular glutamate and decreased energy. As a result, calcium influx results in uncontrolled release of intracellular calcium and subsequent cytotoxic events, including uncoupling of oxidative phosphorylation necessary for ATP. Enzyme systems activated included protein kinase C, the phospholipases (and thus arachidonic acid cascades and platelet-activating factor), and nitric oxide synthase. Oxygen radicals are released, leading to irreversible cell injury and death (Proulx and Dhupa, 1998).

Blood flow to the CNS is well autoregulated through a combination of metabolic, vascular pressure, and oxygen-related mechanisms. Cerebral vasculature and intracranial pressure (ICP) must, however, be functioning normally. Metabolic demands of the brain appear to affect regional blood flow through the effects of pH and adenosine on vascular tone. Increased metabolic activity decreases vascular tone, causing vasodilation. Arterial P_{CO_2} has global control of the brain such that increases result in increased cerebral blood flow (and increased ICP), whereas decreases cause decreased cerebral flow. The potential exists for these reflex responses to exceed (in the case of increase) or to be insufficient (in the case of decrease) for the metabolic needs. Response to P_{CO_2} is regional, complicating the use of hyperventilation as a treatment for increased ICP (Proulx and Dhupa, 1998). Local nitric oxide synthesis plays a role in regional blood flow and can contribute to secondary brain injury.

The cerebral ischemic response is global and depends on an intact vasomotor center. It occurs relatively late in response to poor perfusion. Increased ICP decreases cerebral perfusion. Increased P_{CO_2} causes the vasomotor center to increase heart rate and intense systemic vasoconstriction in an attempt to support cerebral blood flow. Clinically, the increase in systemic blood pressure may cause a decrease in heart rate, an indicator that increased ICP is limiting cerebral blood flow. The lack of the ischemic response does not, however, indicate that ICP increase is not severe; rather, it may reflect vasomotor damage.

Causes of Severe Brain Injury

Primary brain injury occurs as a result of direct brain trauma (Chesnut et al., 1993; Chesnut, 1997; Proulx and Dhupa, 1998). Secondary brain injury reflects damage to the brain as a result of increased metabolic demands inadequate cerebral blood flow, or both. Epilepsy causes the former by increasing metabolic demands (oxygen and glucose). Hyperthermia increases ICP (several millimeters of increase for each degree of increase in body temperature) by increasing metabolic demands. Head trauma tends to cause the latter by increasing ICP. Systemic hypotension also can cause secondary brain injury. Because the patient with severe head injury is less tolerant of derangements in metabolism, both hyperglycemia and hypoglycemia can contribute to secondary damage. Hypoglycemia contributes to decreased ATP production, whereas hyperglycemia can lead to anaerobic glycolysis and cellular acidosis in cells with impaired mitochondrial function.

Cerebral Edema

Cerebral edema can be categorized into a number of forms, each of which can occur after head trauma (Miller, 1993). Vasogenic edema reflects increased permeability of the blood-brain barrier and may be exemplified by focal cerebral contusion and hemorrhage. Water, sodium, and protein increase in the interstitial space. In addition to trauma, causes of vasogenic edema include loss of the tight endothelial junctions (as might occur during infusion of hyperosmotic solutions), tumors, hyperthermia, and epileptic seizures. Mediators associated with vasogenic edema include bradykinin, serotonin, histamine, and the eicosanoids (especially leukotrienes), as well as free oxygen radicals. Drugs that increase cerebral blood flow will increase the rate of cerebral edema. White matter has more compliance, and most of the edema accumulates there.

Cytotoxic edema occurs intracellularly when membrane sodium/potassium ATPase pump mechanisms fail due to lack of energy. Energy loss can reflect decreased cerebral blood flow (i.e., ischemia). Potassium accumulation occurs in the extracellular space. Calcium influx initiates a cascade of events that are lethal to astrocytes. The remaining types of edema might be considered a variation of either vasogenic or cytotoxic edema. Hydrostatic edema reflects accumulation of protein-free fluid in the interstitial tissues. Hydrostatic edema probably results from an abrupt increase in the hydrostatic pressure gradient between the intravascular and extravascular spaces. Osmotic brain edema occurs as serum osmolality (generally due to hyponatremia) declines below a critical threshold. The use of 5% dextrose can contribute to osmotic brain edema. Interstitial edema is exemplified by high-pressure hydrocephalus associated with increased hydrostatic pressure in the ventricular cerebrospinal fluid. Water infiltrates into the periventricular tissues. This type of edema occurs rarely after CNS trauma. Treatment of brain edema includes reversal of the underlying cause, medical management, and surgical decompression.

Increased Intracranial Pressure

The control of increased ICP is paramount in the treatment of head trauma. In humans, approximately 40% of those losing consciousness after a traumatic episode will develop intracranial hypertension, and mortality will parallel increases in ICP. Indeed, ICP is a strong predictor of outcome, and monitoring ICP in human medicine has become a safe and effective tool for monitoring both the need and efficacy of treatment.

Early and aggressive treatment has been shown to improve outcome (Chesnut et al., 1993; Chesnut, 1997). The pressure at which ICP is maintained is not clear, but humans maintained at 15 mm Hg (normal being 20 mm Hg) had an improved outcome compared with those managed at 25 mm Hg. This may reflect the fact that herniation after lesions in some areas can occur despite ICP being normal (20 mm Hg). Recommendations in human medicine are to treat ICP when increased above 20 mm Hg for more than 15 minutes. Hypotension (systolic blood pressure <90 mm Hg) and hypoxia (Pao_2<60 mm Hg) also commonly occur in patients with head trauma and can contribute to increased ICP. Of the two, however, hypotension is more devastating and is predictive of a poorer outcome of severe head injury. Thus hypotension should be avoided and immediately treated when present.

Surgical removal of brain volume is the easiest method (in humans) of lowering ICP. Removal of cerebrospinal fluid is another method (Allen and Ward, 1998). Medical management is faciliated by discriminating the cause of ICP.

Medical Management

Because little information is known regarding the direct treatment of damaged neuronal tissue, treatment focuses on maintaining as normal an environment as possible to support neuronal regeneration. Supportive management focuses on maintaining normal physiologic homeostasis. Blood pressure, arterial oxygenation (pulse oximetry and arterial blood gases), body temperature, and fluid and electrolyte balance should be maintained. Electrocardiographic monitoring also is indicated. Hypotension in particular must be avoided in the patient with increased ICP; the hyperdynamic state (physiologic responses compensating for hypovolemia) will complicate control of ICP. Hyperglycemia can increase metabolism and should be avoided and aggressively managed in the patient with head trauma. Fluids containing dextrose should be avoided in such patients.

Adjuvant Nonpharmacologic Management. Elevation of the head 30 degrees above heart level appears to be beneficial to decreasing ICP (Chesnut et al., 1993; Chesnut 1997; Bagley, 1996). Hypercapnia must be avoided in patients with head trauma; this includes hypercapnia that may be iatrogenically induced during procedures intended to support the respiratory system. Hyperventilation to maintain a $Paco_2$ of 27 to 30 mm Hg can decrease cerebral blood flow and help lower ICP. It is, however, dependent on intact autoregulation. Hyperventilation can decrease the metabolic activities of the brain and induce or potentiate cerebral ischemia. Its effectiveness in diminishing cerebral blood volume decreases with time (at 72 to 96 hours), and a rebound effect with restoration to normocapnia may potentially increase ICP.

Hypocarbia is easy to induce. Its use in the management of increased ICP might be reserved for the initial stages. Later use should be accompanied by strict monitoring of ICP, especially as hyperventilation is discontinued. Profound hyperventilation should be avoided. Hypothermia currently is being investigated for use in the prevention of CNS ischemia associated with severe head injuries (Allen and Ward, 1998). It has been used experimentally in dogs. Mild degrees of hypothermia (between 31° and 35°C) are

Drugs That Modify Animal Behavior 25

Dawn Merton Boothe

- NEUROTRANSMITTERS AND THEIR ROLE IN ABNORMAL BEHAVIORS
- DRUGS USED TO MODIFY BEHAVIORS
- Antipsychotic Drugs
  - Structure-Activity Relationships
  - Pharmacologic Effects
  - Disposition
  - Side Effects and Toxicity
  - Drug Interactions
  - Clinical Indications
- Antidepressant Drugs
  - General Comments
  - Tricyclic Antidepressants
  - Selective Serotonin Re-uptake Inhibitors
  - Monoamine Oxidase Inhibitors
- Anxiolytics
  - Pharmacology
  - Side Effects
  - Clinical Indications
- Anxioselective Drugs: Azapirones (Buspirone)
  - Structure-Activity Relationships
  - Side Effects
  - Clinical Indications
- Miscellaneous (Nonspecific) Drugs Used to Modify Behavior
  - Progestins
  - Anticonvulsants
  - Narcotic Agonists and Antagonists
  - Antihistamines
  - β-Blockers
  - Stimulants
- TREATMENT OF SPECIFIC BEHAVIORAL DISORDERS
- Canine Behaviors
  - Dominance-Related Aggression
  - Stereotypic Motor Behaviors, Obsessive-Compulsive Disorders, Self-Mutilating Disorders
  - Multiple-Animal Households
  - Excessive Barking
  - Destructive Behavior
  - Anxieties, Noise Phobias
  - Sexual Behaviors
  - Psychogenic Dermatoses
  - Hyperactivity
  - Narcolepsy
- Feline Behaviors
  - Inappropriate Elimination
  - Social Behaviors and Aggression
  - Psychogenic Dermatoses
  - Sexual Behaviors

NEUROTRANSMITTERS AND THEIR ROLE IN ABNORMAL BEHAVIORS

Little is known about the cellular mechanisms of abnormal behavior in humans or animals. The most likely neurotransmitters (NTs) associated with abnormal behavior can probably be identified based on the NTs targeted by drugs used to modify the behaviors. These neurotransmitters include the biogenic amines serotonin and histamine (H_1 subtype), the monoamine dopamine, the catecholamine norepinephrine, acetylcholine, γ-aminobutyric acid (GABA), and the excitatory amino acids (Overall, 1997; Simpson and Simpson, 1996).

Among the more effective drugs for modification of behavior are those (e.g., fluoxetine, clomipramine) that tend to be selective for serotonin. Serotonin is synthesized in the brain from tryptophan. There are at least nine serotonin (5-HT) receptor subtypes, four of which appear to be particularly important (Simpson and Simpson, 1996). Serotonin receptors differ in anatomic location and behavioral roles. The 5-HT_1 receptors, located primarily in the brain, are predominantly inhibitory (inhibition of adenyl cyclase) in nature, both presynaptically and postsynaptically. They appear to affect mood and behavior (Overall, 1997). Regulation of serotonin action is complex, involving both presynaptic and postsynaptic mechanisms (Simpson and Simpson, 1996).

Norepinephrine is the end product of dopamine oxidation. Its inactivation occurs primarily by active transport, or re-uptake, into presynaptic vesicles. The NT is then deaminated by mitochondrial monoamine oxidases. Norepinephrine is located predominantly in the gray matter of the pons and in the medulla. Norepinephrine interacts with α_1-receptors (via G protein–mediated activation of phospholipase C and subsequent formation of inositol triphosphate) and β-receptors (via activation of adenylyl cyclase) postsynaptically. Interaction with α_2-receptors (also via G proteins) occurs presynaptically. The behavioral effects of norepinephrine appear to affect arousal, functional reward systems, and mood. The latter effect may reflect a decrease in depression and an increase in mania.

Dopamine is synthesized from L-dopa in presynaptic vesicles, which in turn is produced from dietary tyrosine (Simpson and Simpson, 1996). Tyrosine is first oxidated (by tyrosine oxidase) and then decarboxylated. Dopamine is metabolized by monoamine oxidase (MAO) and catechol-*O*-methyltransferase (COMT). Dopamine receptors are distributed throughout the brain, but less so than norepinephrine. Dopamine appears to be largely located in the midbrain, hypothalamus, and limbic system (the part of the brain thought to control emotions) (Simpson and Simpson, 1996). Dopamine receptors (at least five subtypes) also are found in portions of the extrapyramidal system responsible for coordinated movement (Overall, 1997). At least four dopamine receptors are affected by mood disorders and stereotypies; increased dopamine appears to stimulate these abnormal behaviors (Overall, 1997). Dopamine also is located in selected regions of the limbic system.

γ-Aminobutyric acid is a major inhibitory NT, being active at 30% of synapses in the human central nervous system (CNS). It is formed from glutamate, which is widely distributed throughout the brain. Two primary receptor types, $GABA_A$ and $GABA_B$, appear to cause postsynaptic inhibition by facilitating chloride ion influx into the neuron. Several drugs, including the benzodiazepines and barbiturates (such as phenobarbital), interact with the receptor in an agonistic fashion, causing neuronal inhibition (Overall, 1997). The physiologic and behavioral effects of GABA and its receptors have not yet been well characterized (Simpson and Simpson, 1996).

Excitatory NTs may increase and cause or be associated with several abnormal behaviors, including aggressive, impulsive, and schizophrenic disorders in humans. Among the more important excitatory NTs is glutamate. Glutamate is preformed and stored in synaptic vesicles that are released by calcium-mediated endocytosis. Barbiturates and progesterone modulate behaviors, in part, by inhibiting calcium uptake and thus release of glutamate at the NT (Overall, 1997).

Acetylcholine is the most widely distributed NT in the brain (Simpson and Simpson, 1996). It is produced from choline and rapidly metabolized by acetylcholinesterase. It tends to be an excitatory neurotransmitter. Like glutamate, it is preformed and stored at the terminal end of the synapse in vesicles that are stimulated by calcium to release the NT by exocytosis. The primary significance of acetylcholine and behavior-modifying drugs is the likelihood of adverse reactions occurring when M1 receptors are antagonized (Overall, 1997).

Neurotransmitters tend to be formed and degraded locally. Both formation and inhibition offer pharmacologic targets. A number of drugs result in an increase in the presence of NTs in the synaptic cleft by inhibiting either the metabolism (e.g., dopamine) or the re-uptake (e.g., serotonin, norepinephrine) of the NT after release (Fig. 25–1).

DRUGS USED TO MODIFY BEHAVIORS

Drugs that modify behavior include the antipsychotic drugs (predominantly antidopaminergic in action), anxioselective drugs such as the azapirones (primarily antiserotonergic in action), drugs used to treat affective or mood disorders (antidepressants, lithium, and selected anticonvulsant drugs), and drugs used to treat anxiety and anxiety-related disorders (anxiolytics or minor tranquilizers, benzodiazepines). Other drugs include antihistamines, β-blockers, progestins, anticonvulsants, and opioid antagonists. Most of the drugs used to modify behaviors are used for treatment of other disorders, and as such may be discussed elsewhere in this volume. Only drugs that have veterinary application are discussed here. Table 25–1 provides more specific information about the use of these drugs.

Antipsychotic Drugs

Psychotic disorders in humans involve a severe disturbance of brain function characterized by thought and speech disruption and hallucinations or delusions (Simpson and Simpson, 1996). Although psychotic disorders do not appear to occur in veterinary medicine, drugs developed for their management in humans have proved efficacious for a number of veterinary applications. Antipsychotic drugs (also called *neuroleptics* or *major tranquilizers*) include the phenothiazines, the thioxanthenes (structurally related to the phenothiazines), heterocyclic dibenzepines, the butyro-

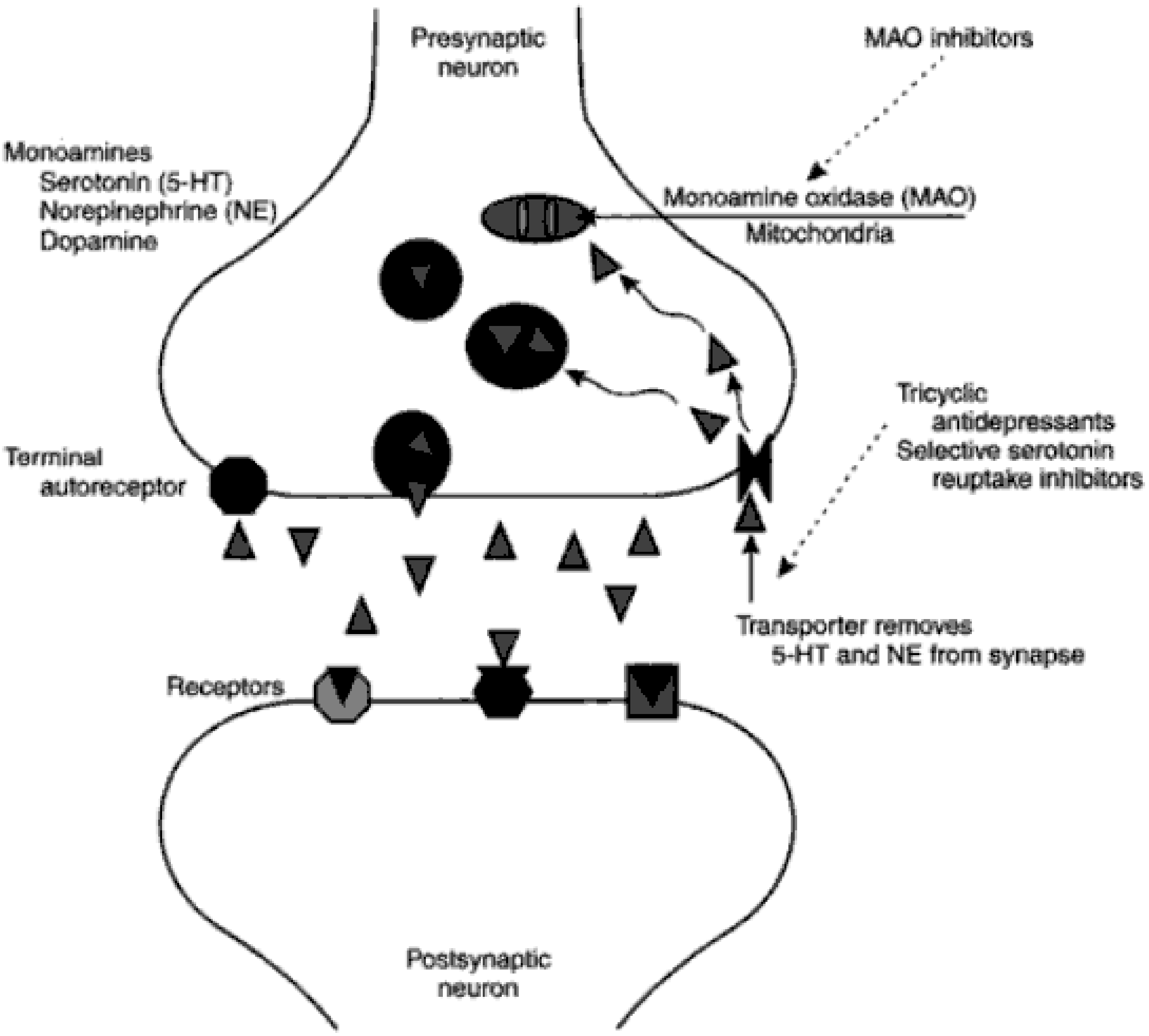


Figure 25–1. Mechanism of action of selected behavior-modifying drugs. Neurotransmitters responsible for behavior are released from the presynaptic neuron into the synaptic cleft and interact with postsynaptic receptors. Following exocytosis, inactivation of the transmitter occurs primarily by re-uptake into the presynaptic neuron, the site of action of most behavior-modifying drugs. Activation also may involve metabolic degradation, as in the case of the monoamines (MOA).

Table 25–1. Drugs Used to Modify Small Animal Behavior

Drug	Class	Dose	Route	Interval (Hours)
Acepromazine	Phenothiazine, sedative	1–2 mg/kg	PO	8
		0.05–0.1 mg/kg	IV, IM	8
Alprazolam	Benzodiazepine, anxiolytic	0.01–0.1 mg/kg (D) (do not exceed 4 mg)	PO	As needed
		0.125–0.25 mg/kg (C)	PO	12
Amitriptyline	TCA	1–4.4 mg/kg (D)	PO	12–24
		0.5–2.0 mg/kg (C)	PO	12–24
Buspirone	Azaperone, anxioselective	2.5–10 mg (not to exceed 2 mg/kg [D])	PO	24
		1 mg/kg (D)	PO	8–12
		0.5–1 mg/kg (C)	PO	8–12
Carbamazepine	Anticonvulsant	400-1600 mg	PO	Divided every 8–12 h
		4–8 mg/kg (D)	PO	8–12
Clomipramine	TCA	1–3 mg/kg (not to exceed 200 mg/day) (D)	PO	12–24, increasing dose at 14-day intervals
		1–5 mg/cat	PO	12–24
		0.5 mg/kg (C)	PO	24
Clonazepam	Benzodiazepine, anxiolytic			
Clorazepate	Benzodiazepine, anxiolytic	0.5–1 mg/kg	PO	12–24
Clorazepate sustained delivery	Benzodiazepine, anxiolytic	11.25–22.5 mg/dog	PO	12–24
Chlordiazepoxide	Benzodiazepine, anxiolytic			
Dextrometamphetamine	Stimulant	2.5–5 mg (medium-sized dog)	PO	12–24
Diazepam	Benzodiazepine, anxiolytic	0.25–1 mg/kg	PO	6–12
Diazepam sustained delivery	Benzodiazepine, anxiolytic	0.5–1 mg/kg	PO	12–24
Doxepin	TCA (antihistaminergic)	3–5 mg/kg (D)	PO	8–12
Fluoxetine	SSRI, antidepressant	1 mg/kg (D)	PO	12–24
		0.5–1 mg/kg (C)	PO	24
Haloperidol	Tranquilizer, Butyrophenone	1-4 mg (D)	PO	12
Hydrocodone	Opioid agonist	0.25 mg/kg (D)	PO	8
		0.25–1 mg/kg (C)	PO	8–12
Hydroxyzine	Antihistamine (H_1)	2.2 mg/kg	PO	8
Imipramine	TCA	2.2–4.4 mg/kg (D)	PO	12–24
Lorazepam	Benzodiazepine, anxiolytic			
Medroxyprogesterone acetate	Progestin	11 mg/kg	IM, SC	Up to 3× per year
Megestrol acetate	Progestin	1–2 mg/kg (up to 4 mg/kg; see text)	PO	24 h for 7–14 days, then decreasing doses by half until discontinued at 3–4 weeks
Methylphenidate	Stimulant	0.25 mg/kg (D)	PO	12–24?
Nalfeme	Opioid antagonist	1–4 mg/kg	IM	
Naloxone	Opioid antagonist	11–22 μg/kg	IV, SC, IM	As needed
Naltrexone	Opioid antagonist	1–4 mg/kg	PO	12–24
Nortriptyline	TCA (metabolite of amitriptyline)	1–2 mg/kg (D)	PO	12
Oxazepam	Anxiolytic, benzodiazepine	0.2-0.5 mg/kg (C)	PO	12–24
Paroxetine	SSRI	1 mg/kg	PO	24
Perphenazine	Phenothiazine, tranquilizer	0.88 mg/kg	PO	8–12
Pindolol	β-blocker	0.124–0.25 mg/kg	PO	24
Propranolol	β-blocker	0.5–2 mg/kg	PO	8
Protriptyline	TCA	5 mg (D)	PO	24, at bedtime
Thioridazine	Phenothiazine	1.1–2.2 mg/kg (D)	PO	12–24

Abbreviations: C = cat; D = dog; IM = intramuscular; IV = intravenous; PO = oral; SC = subcutaneous; SSRI = selective serotonin re-uptake inhibitor; TCA = tricyclic antidepressant.

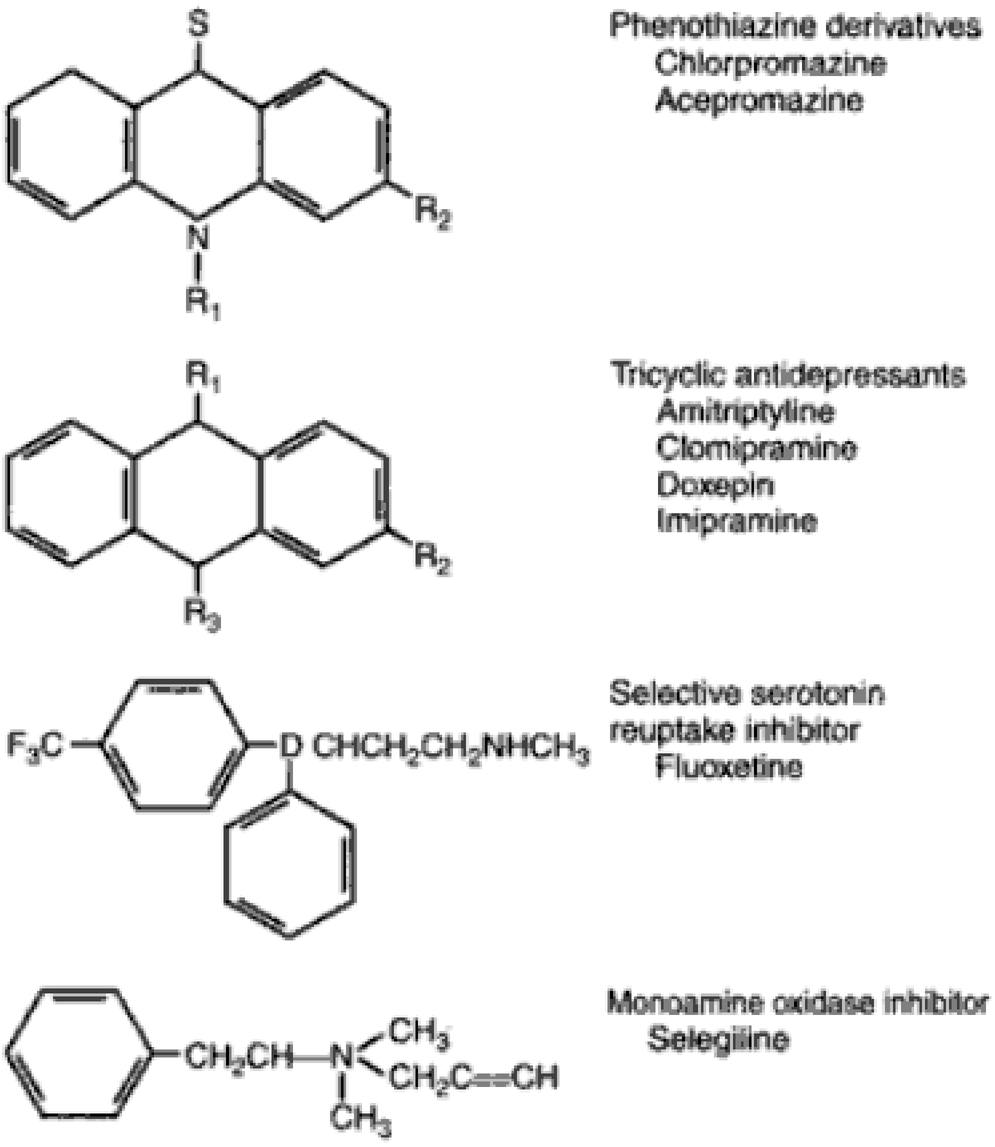


Figure 25–2. Structures of selected behavior-modifying drugs.

phenones, and diphenylbutylpiperidines (Baldessarini, 1995a,b) (Fig. 25–2).

Structure-Activity Relationships

Antipsychotic drugs are categorized by structure and by potency. Low-potency drugs (chlorpromazine, acepromazine, promazine) are characterized by greater sedation and cardiac and anticholinergic side effects compared with their high-potency counterparts. High-potency drugs (e.g., haloperidol, fluphenazine, trifluoperazine, prochlorperazine, and thiothixene) are administered at lower doses and are associated with less sedation and fewer anticholinergic and cardiac side effects. They do, however, have a greater incidence of extrapyramidal side effects.

The largest structural class of antipsychotics is the phenothiazines or tricyclic antipsychotics, which should not be confused with the tricyclic antidepressant drugs (discussed later). The tricyclic antipsychotic drugs are represented by phenothiazine, a three-ring structure containing a sulfur and nitro group in the ring connecting two benzene rings. Substitutions on one of the benzene rings yield different drugs (e.g., chlorpromazine, promazine), which differ in efficacy (see Fig. 25–2). The pharmacology also is impacted by substitutions of nitro groups such that potency (but not efficacy) is reduced by an aliphatic side chain (e.g., chlorpromazine, thorazine, acepromazine, and triflupromazine) (Baldessarini, 1995a,b).

The length of the side chain also determines antihistaminergic properties, with two-carbon side chains such as that occurring in promethazine being more antihistaminergic. Drugs with higher potency have a piperazine side chain, including fluphenazine and rifluoperazone. Esterification with long-chain fatty acids results in long-acting (due to slow hydrolysis and absorption) drugs (e.g., fluphenazine enanthate or decanoate) (Baldessarini, 1995a,b). The use of these latter drugs in small animal veterinary medicine has yet to be established.

The butyrophenone neuroleptics include haloperidol (the prototype) and droperidol. The latter is very short acting and highly sedative; thus its use is limited to anesthetic regimens (Baldessarini, 1995a,b).

Pharmacologic Effects

The pharmacologic effects of antipsychotic drugs generally are similar among humans and animals (Baldessarini, 1995a,b). Phenothiazines are also categorized as tranquilizers. As tranquilizers, the phenothiazines are calming in nature, causing a decrease in spontaneous activity that generally decreases response to external stimuli (Overall, 1997). The predominant antipsychotic action of the phenothiazines is *neuroleptic*, a term derived from the effect of the drugs on human psychiatric patients and intended to contrast with signs typical of CNS depression (Baldessarini, 1995a,b). The neuroleptic effects are attributed, but not conclusively so, to the antidopaminergic effects at D_2 receptors (Baldessarini, 1995a,b).

Some of the neuroleptics (e.g., the phenothiazines) have high affinity for and thus also antagonize D_1 dopamine receptors, although pharmacologic effects at these receptors appear to be minimal. Phenothiazines also block D_3 and D_4 (which are D_2-like) receptors. Selected "atypical" antipsychotic drugs (e.g., clozapine) have a low affinity for D_2 receptors and are not characterized by extrapyramidal effects. They are, however, characterized by α_2-adrenergic antagonism. Some of the antipsychotic drugs also have affinity for serotonergic (5-HT_2) receptors (e.g., clonazepam). Cholinergic and histaminergic (H_1) receptors also are targeted by some of the drugs, resulting in unique pharmacologic effects among the neuroleptics. Variable interactions with different receptor types lead to unpredictable effects on the autonomic system. Among the neuroleptics, chlorpromazine has significant α-adrenergic antagonistic actions. In general, the antimuscarinic actions of neuroleptics are weak.

Neuroleptic effects include suppression of spontaneous movements or complex behaviors but minimal effects on spinal reflexes and unconditioned nociceptive avoidance behaviors. Interest in the environment is minimized, as are manifestations of emotion. Patients are easily aroused; ataxia or incoordination should not be evident at appropriate doses (Baldessarini, 1995a,b). Aggressive or impulsive behavior should gradually diminish. As a result, conditioned avoidance (but not unconditioned escape or avoidance) behavior and exploratory behavior are minimized. Feeding and emesis also are inhibited. At high doses, cataleptic immobility is evident (particularly in cats [Simpson and Simpson, 1996]), resulting in increased muscle tone (and the ability to place animals in an abnormal posture) and ptosis. Akathisia, an increase in restless activity, is an undesirable side effect that occurs in humans but apparently not in animals. Akathisia occurs as an adaptive response to increased phenothiazines in extrapyramidal tissues (Baldessarini, 1995a,b).

Thioridazine has been used in one case of aberrant motor behavior (Jones, 1987).

Antidepressant Drugs

General Comments

Much of the information regarding the use of these mood-modifying drugs in animals has been extrapolated from human use. These drugs are characterized by clinical pharmacology and mechanisms of action that are likely to differ markedly among animals. Yet little scientific information is available to guide their use in animals. Currently, clomipramine is the only one of these drugs approved for use in animals.

Affective (behavior) disorders targeted by antidepressants in people range from depression to manic-depressive disorders. In animals, the list of targeted disorders is much greater and often appears to include any type of behavior deemed "unacceptable" by pet owners. Among the human mood-modifying drugs that have been used in animals are the tricyclic antidepressants (TCAs), the monoamine oxidase (MAO) inhibitors (selegiline), and selective serotonin re-uptake inhibitors (fluoxetine).

To best understand the pharmacologic actions (intended and undesirable) of these drugs, it is necessary to appreciate the extent to which NTs targeted by these drugs are active in the brain. Among the most commonly targeted NTs is the biogenic amine system, with norepinephrine, 5-hydroxytryptamine (5-HT; serotonin), and dopamine serving as primary targets. Acetylcholine and histamine are common although generally secondary targets. In addition, α-adrenergic receptors may be stimulated by some of these drugs. The pharmacologic and side effects of these drugs vary with the NT targeted. Drugs that are more specific in their actions tend to be safer. The ability to predict the effect of antidepressant drugs on behavior reflects in part the inability to predict effects at the synapse as well as a lack of knowledge regarding the impact of neurotransmission on behavior. In general, blockade of dopamine transport appears to be stimulatory rather than antidepressant. Inhibition of serotonin re-uptake appears to be antidepressant. Inhibition of norepinephrine re-uptake consistently yields antidepressant actions.

Tricyclic Antidepressants

Structure-Activity Relationships

The TCAs are among the most frequently prescribed drugs in human behavior medicine. Their name reflects their chemical structure (see Fig. 25–2). The TCAs were identified as a group of potentially useful drugs for the modification of behavior in the 1940s after the generation of a number of drugs with antihistaminergic, sedative, analgesic, and antiparkinsonian effects. Imipramine was selected based on its hypnotic and sedative effects. Imipramine differs from phenothiazine only by the replacement of sulfur with an ethylene bridge, yielding a seven-member ring. This compound proved ineffective in quieting agitated psychotic patients, but very effective for selected mood disorders (Baldessarini, 1995a,b).

The search for chemically related compounds yielded a number of additional drugs. Clomipramine, amitriptyline, and doxepin are all derivatives of imipramine (Baldessarini, 1995a,b). Each contains a tertiary amine at one of the substitution sites on the seven-member ring. Desipramine, a major metabolite of imipramine, and nortriptyline, the *N*-demethylated metabolite of amitriptyline, are secondary amine tricyclics. Protriptyline and trimipramine are other TCAs with few veterinary applications (Simpson and Simpson, 1996). Differences in the effects of NT re-uptake vary with the different amine structures (Baldessarini, 1995a,b).

Mechanism of Action

The mechanism of action of the TCAs (and MAO inhibitors and selective serotonin re-uptake inhibitors [SSRIs]) is blockade of the mechanisms of physiologic inactivation (see Fig. 25–1). For the TCAs, the mechanism is inhibition of re-uptake at presynaptic biogenic amine NT receptors in the brain. As re-uptake is inhibited, the concentration of NTs increases, prolonging their actions (CNS stimulation). Differences in NTs impacted reflect, in part, the chemical structures (Baldessarini, 1995). Imipramine and its derivatives with a tertiary amine side chain block norepinephrine re-uptake but have little effect on dopamine reuptake.

The secondary amine derivatives of imipramine are potent and highly selective inhibitors of norepinephrine re-uptake; however, they are characterized by fewer autonomic and anticholinergic effects. Tertiary amines that are metabolized in the patient to secondary amines will have effects on norepinephrine re-uptake. Clomipramine has marked effects on serotonin re-uptake. Doxepin is characterized by greater antihistaminergic actions (thus explaining its frequent recommendation for chronic pruritus). Although amitriptyline is the most commonly prescribed drug for animals, clomipramine has recently been approved for treatment of separation anxiety in dogs.

Pharmacologic Effects

Adaptation to Pharmacologic Effects. The effects of TCAs at presynaptic and postsynaptic receptors and autoregulation result in complex responses that are not well understood. Although inhibition of re-uptake occurs very rapidly, peak effects still take several weeks. This prolonged time to maximal effect reflects in part disposition (see later discussion of clinical pharmacology) but also appears to reflect adaptation in the CNS to changes in NT concentrations at the synapse. Administration of a TCA results in an immediate decrease in the synthesis and release of norepinephrine or serotonin (depending on the major target of the TCA) in selected areas of the brain. The effects appear to be mediated presynaptically through autoreceptors (α_2 or serotonin, respectively). Turnover, however, gradually normalizes within 1 to 3 weeks. Autoreceptors appear to be down-regulated and become desensitized to the presence of the TCA (Baldessarini, 1995a,b). The number and sensitivity of postsynaptic adrenergic receptors do not appear to be impacted by continued use of a TCA.

Adaptive responses appear to influence the pharmacologic properties of TCAs at adrenergic receptor sites. The TCAs have a moderate affinity for α_1-receptors and only limited affinity for α_2-receptors and β-receptors. Changes in serotonin receptors after repeated treatment with TCAs are complex. Although the impact is not clear, the general effect appears to be increased sensitivity to serotonin. This may be an important component to the outcome of prolonged treatment (Baldessarini, 1995a,b). The TCAs also appear to impact the effect of other NTs and their receptors, including GABA (unknown significance), and dopamine (D_2; desensitization of autoreceptors resulting in mood elevation). Other factors to consider regarding adaptation to TCA effects include changes in AMP-dependent protein kinases and potential changes at the level of gene expression (Baldessarini, 1995a,b).

In addition to tolerance (to sedative and autonomic effects), physical dependence to the TCA can develop. Physical dependence after acute withdrawal is manifested in human patients as malaise, chills, coryza, and muscle aches (Baldessarini, 1995a,b). Slow discontinuation of the drug is recommended.

Autonomic Nervous System. The predominant effect of TCAs on the autonomic nervous system appears to reflect inhibition of norepinephrine transport into adrenergic nerve terminals and antagonism of muscarinic cholinergic and α_1-adrenergic responses to the NTs. Blurred vision, dry mouth, constipation, and urinary retention at therapeutic doses (documented in humans) appear to reflect anticholinergic effects (Baldessarini, 1995a,b).

Cardiovascular System. Cardiovascular effects of TCAs occur at therapeutic doses and can become life threatening with overdose. Postural hypotension occurs in human beings due to α-adrenergic blockade. Mild sinus tachycardia occurs due to inhibition of norepinephrine uptake and muscarinic (M1) blockade (Baldessarini, 1995a,b). Conduction time is prolonged, especially at concentrations above 200 ng/mL. The TCA can also directly suppress the myocardium (Baldessarini, 1995a,b). The myocardial depressant effects are greater in the presence of underlying cardiac disease.

Clinical Pharmacology

The disposition of the TCA favors adverse reactions in that the characteristics of disposition are those that tend to vary greatly among animals, and extrapolation between species is complicated. Unfortunately, the disposition of the drugs has not been scientifically studied in animals, and information is extrapolated from human data. The TCAs are very lipophilic. As such, they are well absorbed after oral administration. They can, however, undergo marked first-pass metabolism. High doses can cause anticholinergic effects on the gastrointestinal tract, slowing absorption or making it erratic. Absorption in humans can result in peak concentrations as rapidly as 2 hours or as long as 12 hours after administration (Baldessarini, 1995a,b). The drugs are very highly protein bound, but unbound drug is characterized by a very large volume of distribution (10 to 15 L/kg in human patients), contributing to a long elimination half-life. Drug may bind avidly to selected tissues.

Drugs are eliminated by hepatic (oxidative) metabolism. Metabolism is variable among human patients, accounting for plasma concentrations that differ by 10- to 30-fold. Metabolism yields active and inactive metabolites. It is not clear what percentage of the antidepressant activity of the TCA is associated with the metabolites. Metabolites generally have an elimination half-life that is twice or more that of the parent compound (Baldessarini, 1995a,b). Thus, accumulation of the metabolites can result in a marked proportion of the pharmacologic effect of TCAs.

Following multiple oral administration in dogs, both clomipramine and its principal active metabolite, desmethylclomipramine, accumulate following repetitive administration in a dose-dependent manner at doses ranging from 1 to 4 mg/kg (King et al., 2000a). The parent compound has an elimination half-life of 5 to 6 hours compared to 3 hours for the metabolite, resulting in concentrations of the parent compound that are higher than that of the metabolite. Steady-state concentrations are reached in 4 days, resulting in a response within 1 to 2 weeks. Food does not appear to alter the rate or the extent of oral absorption (King et al., 2000b), with bioavailability of clomipramine being 20% and of its metabolite, 140%. Protein binding of both the parent compound and its metabolite are >96%.

Side Effects

Up to 5% of human patients receiving a TCA react adversely. Sedation is common with the TCAs (Simpson and Simpson, 1996). The most common reactions reflect antimuscarinic effect or overdosing. Cardiac toxicity is a less frequently reported but serious effect (with the exception of clomipramine in dogs). Side effects include dry mouth, gastric distress, constipation, dizziness, tachycardia or other arrhythmias, blurred vision, and urinary retention (particularly problematic in the presence of prostatitic hypertrophy) (Baldessarini, 1995a,b). Weakness and fatigue reflect CNS effects. Cardiac toxicity is more likely in patients who start therapy with cardiac disease. In healthy patients, the most likely cardiac response is hypotension due to α-adrenergic blockade.

An undesirable side effect of antidepressant drugs in people is referred to as the "switch process." Patients undergo a transition from depression to hypomanic or manic excitement (Baldessarini, 1995a,b). This effect has not been reported in animals. Confusion and delirium are behavior aberrations that occur commonly in human patients, with the incidence of 10% in all patients, increasing to more than 30% in elderly patients over age 50 years (Baldessarini, 1995a,b). Miscellaneous toxic effects in human patients include leukopenia, jaundice, and skin rashes. Weight gain occurs, particularly with those drugs that are selective for serotonin re-uptake. Isolated reports that address the side effects of TCAs in dogs are uncommon. Goldberger and Rapoport (1991) reported side effects in 5 of 13 dogs receiving clomipramine for lick granuloma. Clinical signs included lethargy, anorexia, diarrhea, and growling.

Acute poisoning with TCAs is common in human patients (accidental or intentional) and appears to be a significant problem in animals (Johnson, 1990). Symptoms in humans vary and are complex. Excitement and restlessness may be accompanied by myoclonus or tonic-clonic seizures. Coma may rapidly develop, associated with depressed expiration, hypoxia, hypothermia, and hypotension (Baldessarini, 1995a,b). Anticholinergic effects include mydriasis, dry mucosa, absent bowel sounds, urinary retention, and cardiac arrhythmias, including tachycardia. Clinical signs reported after accidental ingestion in animals (Johnson, 1990) include hyperexcitement and vomiting as early manifestations, followed by ataxia, lethargy, and muscular tremors. Bradycardia and other cardiac arrhythmias occur later. These later signs occurred shortly before death in experimental animal models of TCA toxicosis (Johnson, 1990).

Treatment for TCA toxicosis is supportive, including respiratory (intubation) and cardiovascular support. Gastric lavage with activated charcoal can be used early. Emetics probably should be avoided because of the risk of aspiration pneumonia in seizuring animals (some anti-emetics may further predispose the animal to seizures). Short-acting barbiturates (or similar drugs) without pre-atropinization are preferred for anesthetic control during gastric lavage. Cathartics (sorbitol or sodium sulfate—Glauber's salt) can be of benefit. Magnesium sulfate should not be used because impaired gastrointestinal motility can facilitate absorption of magnesium. Resolution of coma may require several days; the threat of cardiac arrhythmias likewise persists for several days. Pharmacologic interventions for cardiac arrhythmias have not been well established. Alkalinization (sodium bicarbonate sufficient to maintain blood pH above 7.5: 2 to 3 mEq/kg over 15 to 30 minutes IV) may prevent death by increasing protein binding and increasing cardiac automaticity (due to potassium shifts) (Johnson, 1990). Cardiac drugs, including antiarrhythmics and digoxin, are contraindicated in human patients. Phenytoin may provide antiarrhythmic effects and in human patients is useful for treatment of seizures (Baldessarini, 1995a,b). This latter effect is not likely to occur safely in animals. Diazepam is indicated for acute management of seizures. β-Adrenergic receptor antagonists and lidocaine may be useful (Baldessarini, 1995a,b). The risk of tonic-clonic seizures is increased in human patients, particularly at high doses.

Clomipramine generally is associated with less sedation than with the other TCAs (Juarbe-Diaz, 1997a).

Indications

The TCAs have been recommended among animal behaviorists for most abnormal behaviors manifested in dogs or cats. These include, but are not limited to, behaviors associated with fear and aggression (Juarbe-Diaz, 1997a,b), stereotypes, obsessive-compulsive or self-mutilation disorders, and excessive barking.

Contraindications

The TCAs should be avoided in animal with a metabolic disease. Specific contraindications include a history of cardiac or hepatic disease, seizures, glaucoma, hyperthyroidism, and thyroid hormone supplementation (Juarbe-Diaz, 1997a,b).

Drug Interactions

The TCAs can interact with a number of other drugs. Competition for protein-binding sites with other highly protein-bound drugs can result in increased drug concentrations. Drugs that impact drug-metabolizing enzymes, through either inhibition or induction, also impact the clearance of TCAs. The sequelae of the impact are difficult to predict because active metabolites similarly are impacted. In general, however, drugs that inhibit metabolism are likely to result in greater drug accumulation and increased risk of toxicity. The tricyclic and other antidepressants also can compete with other compounds for metabolism. The drugs themselves may impact metabolism of other drugs. Clomipramine inhibits the metabolism of other drugs (Baldessarini, 1995a,b). The antidepressants potentiate the effects of sedative drugs. The TCAs should not be used in combination with other drugs that modify CNS NTs. Included are monoamine oxidase inhibitors and amitraz (Juarbe-Diaz, 1997a,b). In human patients, a potentially lethal interaction has been reported when a TCA, particularly one that inhibits serotonin uptake, is combined with an MAO (Baldessarini, 1995a,b). The term *serotonin syndrome* has been applied to this interaction, which is characterized by restlessness, muscle twitches, hyper-reflexia, shivering, and tremors.

Clinical Use

Most drugs take 2 to 3 weeks for clinical efficacy to be realized. The exception might be amitriptyline, which may cause a response within 3 to 5 days (Juarbe-Diaz, 1997a). Dogs can resond to clomipramine within 1 to 2 weeks. Therapeutic drug monitoring may facilitate the safe and effective use of the drugs. In human patients, plasma concentrations that range between 100 and 250 ng/mL are most likely to cause satisfactory antidepressant effects; toxicity can be expected at concentrations above 500 ng/mL, with fatal consequences likely as concentrations approach 1000 ng/mL (Baldessarini, 1995a,b). Variability among human patients (and presumably among animals) supports the use of monitoring to guide therapy. Monitoring to avoid toxicity is, however, complicated by the recognition that serum concentrations by themselves are not reliable predictors of toxic responses.

Because of the risk of withdrawal due to physical dependence, discontinuation of TCA should occur over a week or longer if therapy has been prolonged (Baldessarini, 1995a,b).

Selective Serotonin Re-uptake Inhibitors

Structure-Activity Relationships and Mechanism of Action

The SSRIs enhance CNS serotonin by blocking presynaptic neuronal uptake (see Fig. 25–1). They may also increase postsynaptic receptor sensitivity (Simpson and Simpson, 1996). Drugs currently approved in humans include fluoxetine, paroxetine, sertraline, and fluvoxamine. Because of their selectivity for serotonin uptake, the diverse effects that characterize TCAs are generally absent with SSRIs.

Clinical Pharmacology

The clinical pharmacology of the SSRIs is similar to that of the TCAs, including oral absorption, lipophilicity, protein-binding, and volume of distribution. Like the TCAs, fluoxetine is metabolized by the liver to an active metabolite (norfluoxetine) and inactive metabolites (Baldessarini, 1995a,b). The active metabolite is very long acting. In addition, it interferes with the metabolism of other antidepressants, including the TCAs, prolonging their elimination even when the parent drug is no longer present. The elimination half-life of norfluoxetine is 150 to 200 hours in people, compared with 50 hours for the parent compound. Thus, based on accumulation alone, the metabolite can have a profound impact on therapeutic effect. Paroxetine and fluvoxamine have no active metabolites (in human patients). The time to efficacy of SSRIs (which is up to 3 weeks in human patients) reflects, in part, the time for maximum accumulation of the parent drug and its metabolites.

The use of monitoring to guide therapy was addressed with the TCAs. As with the TCAs, effective concentrations have not been established in animals but must be extrapolated from people. The relationship between plasma drug concentrations and therapeutic efficacy has not been well established (Simpson and Simpson, 1996). Plasma concentrations thought to be effective for human patients range from 100 to 300 ng/mL for fluoxetine (and its active metabolites). Effective concentrations for paroxetine and sertraline are 30 to 100 and 25 to 50 ng/mL, respectively (Baldessarini, 1995b).

Drug Interactions

The SSRI can inhibit the metabolism of other drugs; the order of potency of inhibition is paroxetine>norfluoxetine>fluoxetine=sertraline. Because of the risk of drug interactions, SSRIs should not be used in combination with other antidepressants (see earlier discussion of serotonin syndrome and drug interactions of TCAs and MAO inhibitors) (Baldessarini, 1995b).

Side Effects

Compared with the TCAs, SSRIs appear to be safe. Unlike the TCAs, SSRIs have minimal effects on the cardiovascular system (Baldessarini, 1995b). Their safety for patients with underlying cardiac disease has not, however, been established. Sedation is not a common side effect, being least likely with fluoxetine (Simpson and Simpson, 1996). In humans, gastrointestinal side effects are the most common, occurring in as many as 25% of patients receiving the drug (Simpson and Simpson, 1996). Their incidence is minimized by starting with a low dose and gradually increasing the dose until efficacy is evident. Side effects have been reported in animals. In 4 of 14 dogs in a study of fluoxetine for the treatment of lick granuloma (Rapoport et al., 1992), side effects included lethargy, anorexia, and hyperactivity. Another study (Melman, 1995) reported the same side effects as well as polydypsia, diarrhea, and increased or decreased appetite. At least 50% of animals appeared to develop some type of side effect, although side effects were described as "mild." Side effects reported by owners in a study of fluoxetine for treatment of canine dominance-related aggression included fatigue, lethargy, and decreased appetite (Dodman and Mertens, 1995).

Clinical Indications

Probably no behavior-modifying drug has received more attention in the veterinary and lay literature than fluoxetine (Kauffman, 1994; Marder, 1995). Despite the plethora of opinions or testimonials regarding the efficacy of this drug for treatment of animal behavioral disorders, few scientific studies exist. Efficacy for treatment of lick granulomas is supported by a double-blind crossover study (Rapoport et al., 1992). One third of the animals studied did not repeat the abnormal behavior when fluoxetine was discontinued. Fluoxetine also has been studied in an open (nonblinded) study of dogs with a variety of behavioral problems (Melman, 1995). Approximately 65% of dogs with lick granuloma, 100% of animals with separation anxiety, and 85% of animals with tail mutilation disorders responded to fluoxetine. Unfortunately, data were not controlled for other treatments, making interpretation of the success of fluoxetine in this study difficult. Fluoxetine also has been used successfully to treat psychogenic alopecia in a cat (Hartmann, 1995) and dominance aggression in dogs (Dodman and Mertens, 1995).

Monoamine Oxidase Inhibitors

Structure-Activity Relationships

The recognition that the antitubercular drug isoniazid tended to elevate the mood of patients receiving the drug for treatment of tuberculosis led to further discovery of drugs that inhibit MAO. The first drugs used were structurally related to hydrazine and were associated with marked hepatotoxicity. An attempt was made to synthesize CNS-stimulant compounds unrelated to hydrazine but similar to amphetamine. Ultimately, selegiline was a result of this later effort (Baldessarini, 1995a,b).

The MAO inhibitors potentially affect a variety of monoamines by inhibiting mitochondrial MAO and the subsequent degradation of monoamines, most notably dopamine (see Fig. 25–1). Most of the clinically relevant drugs are nonselective toward two major enzyme groups (Baldessarini, 1995a,b) that are characterized by different substrate specificities. MAO-A prefers serotonin and is inhibited by clorgyline, and MAO-B prefers phenylethylamine and is inhibited by selegiline. Selegiline is the only currently used MAO inhibitor characterized by selectivity. The drug targets MAO-B and is relatively selective for dopamine. It is approved for use in dogs for treatment of pituitary-dependent hyperadrenocorticism (purported to be a dopamine deficiency) and cognitive dysfunctions. Binding to the MAO is irreversible, and recovery from effects requires synthesis of new enzyme. In human patients, this appears to require 1 to 2 weeks. Metabolism occurs more slowly in geriatric patients (Baldessarini, 1995a,b).

Pharmacologic Effects

The effects of the MAO inhibitors occur on systems affected by sympathomimetic amines and serotonin. Although as a class the MAOs inhibit a number of enzyme systems other than MAO, generalizations to the class do not necessarily apply to selegiline. Selegiline potentiates dopamine in selected neurons and has been approved to treat Parkinson's disease in humans and cognitive dysfunctions in animals, conditions assumed to be associated with dopamine deficiency. Selegiline also scavenges oxygen radicals and reduces neuronal damage due to reactive products of oxidative metabolism of dopamine or other compounds (Baldessarini, 1995a, b). A delay in the therapeutic effect up to 2 or more weeks characterizes the use of selegiline. Reasons for the delay are not known (Baldessarini, 1995a,b).

Clinical Pharmacology

The MAOs are readily absorbed after oral administration. Maximal inhibition occurs within 5 to 10 days. Despite a long biologic activity, efficacy appears to decrease in human patients if the drugs are administered at an interval longer than 24 hours (Baldessarini, 1995a,b).

Side Effects and Drug Interactions

Selective MAO inhibitors appear to be safe. Severe and potentially fatal interactions have, however, been described when MAO inhibitors were combined with other antidepressants. Particularly problematic is the combination of MAO inhibitors with drugs that inhibit the re-uptake of serotonin (see earlier discussion of serotonin syndrome with TCAs). Other drugs with which MAO inhibitors may interact include meperidine and precursors of biogenic amines. Selective MAOs such as selegiline are not necessarily safer than the older or nonselective inhibitors when combined with other drugs. Hypertensive crisis, a serious side effect that occurs when aged cheeses containing tyramine (a bacterial monoamine by-product) are ingested in the presence of nonselective MAO inhibitors, does not occur with selective MAO inhibitors such as selegiline.

Anxiolytics

Pharmacology

The primary anxiolytics used in veterinary medicine are the benzodiazepines (see Chapters 24, 26), including diazepam, its metabolite oxazepam, clorazepate (metabolized in the stomach to *N*-desmethyl diazepam, a major metabolite of diazepam), lorazepam, alprazolam, and clonazepam. The assumed mechanism of action of these drugs is GABAminergic through interaction with the GABA_A receptor. The anxiolytic effects are separate from the general CNS depressant effects caused by these drugs. Their central effects are somewhat dose dependent. Sedative effects occur at low doses; as a result, excitement is tempered. Antianxiety effects are evident at moderate doses, being beneficial to social interactions. At high doses, hypnotic effects become evident. Sedation becomes profound at high doses, ataxia is evident and sleep is facilitated (Overall, 1997). Decreased skeletal muscle activity—particularly of value in seizuring animals—is central in nature and is independent of sedative effects. Cats appear to be more prone than dogs to muscle relaxation (Overall, 1997). Benzodiazepines may distribute differently cats, with extensive binding of diazepam and its major metabolite, desmethyldiazepam, in the brain (Placidi et al., 1976).

The effects of the benzodiazepines reflect in part metabolism to active, inactive, and potentially toxic metabolites. If efficacy reflects formation of an active metabolite (e.g., desmethyldiazepam), accumulation may be necessary before maximum effects are seen. Lorazepam and oxazepam have short elimination half-lives in human patients and are metabolized by phase II (glucuronidation) enzymes. Thus, metabolites of these drugs are not likely to be active or toxic, although the risk of toxicity in cats has not been assessed.

The elimination half-life of many benzodiazepines in general is short. Efficacy can be prolonged by metabolism to active metabolites (in humans). Slow acting compounds include clorazepate and midazolam. Intermediate half-life drugs such as oxazepam, lorazepam, chlordiazepoxide, and alprazolam have no active metabolites. Longer acting benzodiazepines include diazepam and clonazepam. Alternatively, clorazepate is available as a sustained-release product that can be administered less frequently.

Tolerance develops to the anticonvulsant and sedative effects of many benzodiazepines. Tolerance appears less likely to develop to the anxiolytic effects of these drugs (Simpson and Simpson, 1996). In contrast, withdrawal can accompany rapid discontinuation of the drug. Thus, doses gradually should be tapered (e.g., 25% per week) as the drug is discontinued (Simpson and Simpson, 1996; Overall, 1997).

Side Effects

In addition to changes in behavior, the benzodiazepines have been associated with a number of side effects in human patients. Reaction may be to the parent drug or a metabolite. Long-term use in human patients has been associated with neutropenia and liver disease. Recently, acute fulminating hepatotoxicity has been reported in cats receiving diazepam orally (Center et al., 1996). Clinical signs include anorexia, vomiting, lethargy, hypothermia, and jaundice. The adversity appears to be dose dependent (and thus may be idiosyncratic), occurring in most animals within 5 to 11 days after therapy is begun. Mortality is high (8 of 11 cats in one report) despite intensive therapy. Histology revealed severe acute to subacute lobular to massive hepatic necroses, suppurative cholangitis, and biliary hyperplasia. Baseline hepatic function data might be collected from cats before therapy is begun and again 3 to 5 days after therapy is begun in order to minimize the damage induced by diazepam administered to cats at risk. Any evidence of illness (or evidence of prolonged elimination) should lead to discontinuation of the drug. Clorazepate used in combination with phenobarbital in dogs for control of seizures has, in the author's experience, also been associated with liver disease.

Clinical Indications

The benzodiazepines are less desirable as behavior-modifying drugs because of their nonspecific nature (Overall, 1997). Thus, a notable disadvantage of the long-term use of benzodiazepines is their tendency to interfere with the ability to learn in animals undergoing behavior modification as part of their treatment program (Lindell, 1997). An exception can be made for chlordiazepoxide, which appears to facilitate operant conditioning in nervous dogs (e.g., pointer) (Simpson and Simpson, 1996). Paradoxical reactions may occur in some animals, including rage, hyperexcitability, and anxiety. In addition, the risk that pet owners may use the animal's drug should lead to close scrutiny of the animal's drug needs and use.

Benzodiazepines are indicated for the treatment of anxiety. Alprazolam and clonazepam may be associated with fewer side effects and might be preferred (Overall, 1997); however, fewer reports exist regarding their use in animals. The benzodiazepines are contraindicated in aggressive patients (Overall, 1997). Simpson and Simpson (1996) noted that the contraindication may depend on the cause of aggression. If aggression is a manifestation of an underlying fear or anxiety, then the benzodiazepines may reduce aggression. If, however, anxiety or fear is masking aggression, the benzodiazepine may increase aggression. Other indications for benzodiazepines include treatment of inappropriate elimination (Overall, 1997), noise phobias, and selected anxieties such as visits to the veterinarian (Simpson and Simpson, 1996; Overall, 1997).

Anxioselective Drugs: Azapirones (Buspirone)

Structure-Activity Relationships

Buspirone also is referred to as a nonspecific anxiolytic. Members of this group were specifically developed for atypical depressions, nonspecific generalized anxiety disorders, and selected obsessive-compulsive disorders. Buspirone is the first nonsedating antianxiety drug to be marketed (Simpson and Simpson, 1996). Its effects appear to reflect blockade of 5-HT$_1$ receptors at both presynaptic and postsynaptic sites. Presynaptic inhibition increases serotonergic activity when serotonin is low, whereas postsynaptic control reduces serotonin when it is high (Simpson and Simpson, 1996). Buspirone will cause down-regulation of 5-HT receptors. In addition, it will act as a dopamine agonist throughout the brain (Simpson and Simpson, 1996).

Side Effects

In contrast to benzodiazepine anxiolytic drugs, buspirone has no sedative, muscle relaxant, or anticonvulsant actions. It does not impair motor performance (Simpson and Simpson, 1996). Side effects to buspirone manifested in cats include increased aggressiveness (toward other household cats), increased affection toward owners, mild sedation, and agitation (Cooper, 1997). Vomiting and tachycardia also have been reported (Cooper, 1997). In contrast to the anxiolytic drugs and tricyclic antidepressants, buspirone is associated with a low abuse potential. Withdrawal symptoms after discontinuation of the drug apparently do not occur (Overall, 1997). Abuse potential is very low.

Clinical Indications

Buspirone has been used to treat canine aggression, canine and feline stereotypic behaviors, self-mutilation, obsessive-compulsive disorders, thunderstorm phobias, and feline spraying (Overall, 1997). Buspirone apparently has been particularly useful for treatment of anxiety associated with social situations such as aggression or marking behaviors (Overall, 1997). One week of therapy may be sufficient to evaluate the drug.

Miscellaneous (Nonspecific) Drugs Used to Modify Behavior

Progestins

Progestin interaction with GABA receptors is 10 to 50 times more potent than that of barbiturates (Overall, 1997). This may account for the nonspecific calming effects of the drugs observed in veterinary medicine. The advent of newer behavior-modifying drugs (e.g., TCAs, SSRIs) and the incidence of side effects largely limits their use in animals that have failed other medications and are faced with euthanasia.

Several side effects have been well-documented in animals receiving progestins long term. Among the more notable because of their magnitude or life-threatening nature are gynecomastia, mammary gland neoplasia, diabetes mellitus, aplastic anemia, and pyometra (Juarbe-Diaz, 1997a,b). Animals should be monitored frequently for evidence of adversities.

Progestins are most wisely reserved for adjuvant short-term therapy until the second drug takes effect (i.e., 4 to 6 weeks), and only the oral form is recommended. The progestins also are an alternative for animals in whom euthanasia is being considered; in such cases, a high dose (4 mg/kg orally every 24 hours) has been recommended in order to stimulate a rapid response (Juarbe-Diaz, 1997a).

Anticonvulsants

A number of anticonvulsant drugs have been used to treat behavioral abnormalities. The most notable used for animals include the barbiturate phenobarbital (and its congener primidone) and phenytoin, a hydantoin derivative. Their use has been somewhat efficacious for treatment of overactive or aggressive behaviors (which actually may have been an expression of psychomotor epilepsy) (Overall, 1997). Efficacy is, however, generally dependent on administration of sedative (and, with long-term use, potentially toxic) effects. More notably, their use has largely been replaced by the TCAs or SSRIs. The side effects of these drugs (discussed in Chapter 24) limit their long-term use, although monitoring (as with anticonvulsant therapy) may help avoid toxicity.

Phenytoin has been useful for the treatment of explosive aggression in human patients. Phenobarbital may prove useful for controlling excessive feline vocalization during car travel (Overall, 1997) or canine aggression (Dodman and Shuster, 1994). Carbamazepine (an iminodiabenzyl derivative of imipramine) also has been used to treat explosive aggression in humans. Valproic acid may be useful for treatment of aggression (Dodman and Shuster, 1994).

Narcotic Agonists and Antagonists

The drugs are discussed more in depth for pain control (see Chapter 22). The antagonists in particular have proved useful in the treatment of selective obsessive-compulsive disorders in humans. Efficacy also has been reported to treat selected self-mutilation disorders in dogs (e.g., acral lick dermatitis or lick granuloma) (Overall, 1997; Dodman and Shuster, 1994; Simpson and Simpson, 1996). Pure antagonists, including naloxone and naltrexone, the latter an orally bioavailable product, and mixed agonists/antagonists such as pentazocine appear effective. These drugs block mu and kappa receptors. The assumed mechanism of action is blockade of self-reward mediated by endogenous opioid release that may accompany self-destructive behavior. Hydrocodone also has proved effective in selective self-destructive behaviors in both the dog and cat.

Antihistamines

The mildly sedative (e.g., with hydroxyzine) or hypnotic (e.g., with diphenhydramine) effects caused by H_1 receptor blockade can be of benefit for some behavioral disorders. These drugs are discussed more in depth as antiemetics at the vestibular apparatus (see Chapter 27). Indications as behavior-modifying drugs might include the treatment of chronic pruritus, late-night activity, car travel, and selected transient behaviors accompanied by pacing and vocalization (Overall, 1997).

β-Blockers

β-Adrenergic blockers (e.g., propranolol, pindolol) have been used in human medicine for the treatment of aggressive outbursts associated with self-mutilation or injury problems, intermittent explosive behaviors, conduct disorders, dementia, and schizophrenia (Overall, 1997). The use of these drugs for similar disorders in animals has not, however, been very successful (Overall, 1997). Non-selective β-blockers also have been used to treat anxiety in human beings. One animal behaviorist reports success with propranolol or pindolol (the latter also affecting serotonin receptors) for the treatment of fear aggression in dogs (Dodman and Shuster, 1994).

Stimulants

Stimulants include dextroamphetamine, methylphenidate (Ritalin), and pemoline. Stimulants are characterized by paradoxical effects in that they cause excitement in the normal patient but a calming effect in the hyperactive patient. Their indication for human patients is for the treatment of attention deficits. Conditions of hyperactivity are rare in veterinary medicine. Proper diagnosis is imperative to successful therapy with stimulants.

Their actions are to increase sympathomimetic stimulation. Side effects include increased heart and respiratory rate and anorexia. Tremors and hyperthermia may occur. The drugs are contraindicated for patients with cardiovascular disease, glaucoma, and hyperthyroidism. The drugs should not be used in combination with other behavior-modifying drugs (Overall, 1997).

TREATMENT OF SPECIFIC BEHAVIORAL DISORDERS

Care must be taken to distinguished behavior that is perceived to be abnormal by the pet owner from normal behavior. Pharmacologic management of abnormal behavior should be approached as an adjunct, and specifically as a facilitator, to normalizing behavior rather than as a cure. A number of non-drug techniques have been recommended by many animal behaviorists (Landsberg, 1994; Voith and Borchelt, 1985a,b; Simpson and Simpson, 1996; Houpt, 1997). Abnormal behaviors that require drug therapy should be simultaneously managed with behavior modification training. For example, decreasing arousal and fear can facilitate learning a new behavior (Juarbe-Diaz, 1997a,b). The use of behavior-modifying drugs is not well studied in cats and dogs, and rarely are recommended indications based on well-controlled clinical trials. In addition, many of the drugs used to modify behavior can cause serious side effects, and the clinical pharmacology of the drugs increases the likelihood of adversity because of unpredictability of plasma or tissue drug concentrations. Many of the side effects may not be readily observed by the pet owner, further increasing the risk of side effects. Finally, slow response to therapy may lead to unsupervised manipulation of dosing regimens by the pet owner, again predisposing the animal to adverse reactions. Owners should be well counseled regarding the risks and benefits of behavior-modifying drugs, including potential changes in behavior that may be less desirable than the behavior targeted by the drug. Although many drugs recommended for use in dogs and cats are approved for human, but not veterinary, use, behavior-modifying drugs stand out as having potential risks of adversity (Johnson, 1990). Acquisition of informed owner consent may be prudent before implementing therapy with these drugs. Caution should be taken to avoid substance abuse by pet owners.

Monitoring serum drug concentrations may be of benefit for selected drugs. Monitoring must, however, be performed in conjunction with clinical response, including both efficacy and safety. Antidepressants should be used cautiously or not at all for patients suffering from metabolic illnesses. Adequate time must be allowed before a drug or a dosing regimen is considered to fail. At least two drug elimination half-lives plus the time described to maximum efficacy for the particular drug should elapse. In general, combinations of behavior-modifying drugs should be avoided. One drug should be withdrawn, often slowly, before another is begun. A drug-free time of two drug elimination half-lives is recommended in humans before a new drug is begun. Generally, 10 to 20 days should elapse until a drug-free period has been sufficiently long for a short-acting drug and up to 6 to 8 weeks for longer acting drugs (Overall, 1997).

The following description of drug therapy for selected behaviors is not intended to be a "cookbook" approach to managing abnormal behavior in dogs and cats. Rather, clinicians should familiarize themselves with the assumed behavior and its proper non-drug behavioral modification management. Clinicians should be thoroughly familiar with the drug to be used. Because indications are less clear with these drugs, an emphasis should be placed on side effects, drug interactions, and contraindications. Consultation with a veterinary behaviorist is strongly recommended before implementing any drug therapy.

Canine Behaviors

Dominance-Related Aggression

Aggression appears to be related to noradrenergic, dopaminergic, and serotonergic receptors; of these, the serotonergic appear most important. As such, drugs that are selective for serotonin receptors may be more effective for aggression. Among the TCAs, clomipramine would be preferred. Fluoxetine, paroxetine, and sertraline are selective for serotonin uptake; among these, fluoxetine has been used in dogs for dominance aggression (Dodman et al., 1996). Fluoxetine (1 mg/kg orally 24 hours) significantly decreased owner-directed aggression in a single-blind crossover study (compared with placebo); behavioral modification was not included with drug therapy (Dodman and Mertens, 1995).

Administration of tryptophan, a serotonin precursor, has been associated with reduced aggression. Other drugs that may reduce aggression include propranolol (episodic aggression in people), carbamazepine, lithium, and phenobarbital (Reisner, 1997). Long-term adverse effects outweigh the potential behavior-modifying effect of progestin administration for aggression. Anxiolytic drugs may reduce dominance-related aggression if aggression is a manifestation of fear or anxiety (Simpson and Simpson, 1996; Marder, 1991). Aggression may worsen in some patients treated with benzodiazepine derivatives, however, especially if normal inhibitory mechanisms are suppressed (Simpson and Simpson, 1996). In human patients, anticonvulsants have been useful for treatment of "explosive" aggression. Phenytoin and carbamazepine both have been used. For animals, carbamazepine is preferred for profound aggression that has not responded to other therapy (Overall, 1997). Monitoring may facilitate successful therapy; concentrations known to be effective for control of seizures in human patients (6 to 10 μg/mL) may be effective for control of aggression in animals (Overall, 1997).

Stereotypic Motor Behaviors, Obsessive-Compulsive Disorders, Self-Mutilating Disorders

Stereotypies are repetitive behaviors that appear pointless and mindless to the observer (Dodman and Shuster, 1994). They are generally associated with chronic conflict, confinement, and sensory deprivation. Obsessive-compulsive disorders (OCDs) are poorly defined in veterinary medicine. In humans, OCDs are ritualistic and sufficiently invasive either cognitively or physically to interfere with normal function (Overall, 1994a, 1997). Abnormal behaviors in animals that might be considered OCD include stereotypic, ritualistic circling, spinning, pacing, howling, flank sucking, and fly biting; selected ingestive behaviors; and self-mutilation or grooming behaviors, including acral lick granuloma (Shanley and Overall, 1992; Overall, 1994a, 1997). In humans, the disorders may reflect aberrant serotonin metabolism. Treatment, therefore, has focused on serotonergic metabolism. A similar approach seems to work with dogs with OCD. A series of cases of obsessive-compulsive behaviors in dogs provides evidence of the potential efficacy of clomipramine but not amitriptyline (Overall, 1994a, 1997). Other reports support the use of clomipramine for treatment of OCD (Thornton, 1995; Goldberger and Rapoport, 1991). One single-blind crossover study of lick granuloma found clomipramine but not desipramine to reduce licking by 50% in half of patients studied (Goldberger and Rapoport, 1991). Another clinical report noted the efficacy of clomipramine, but not diazepam, naloxone, or phenobarbital, in a single dog affected with self-trauma (Thornton, 1995).

Fluoxetine has proved useful in several studies for treatment of OCD or self-mutilation, including acral lick granuloma (Melman, 1995; Rapoport et al., 1992) and tail mutilation (Melman, 1995).

The phenothiazine derivative thioridazine was reported useful in one case of aberrant motor behavior (Jones, 1987).

Narcotic antagonists also have been reported to be effective for stereotypic behaviors in dogs manifested as self-mutilation acral lick dermatitis. Release of endogenous opioids may serve as a "reward" system following mutilation. Breaking the reward cycle with antagonists may resolve the behavior (Shanley and Overall, 1992; Dodman and Shuster, 1994). Both naltrexone and nalmefene, pure opioid antagonists, were found to be useful. In one study, self-mutilation activity significantly decreased in 7 of 11 dogs and was partially effective in 3 more (Dodman et al., 1988). Based on accompanying pharmacokinetic studies, concentrations of 20 to 50 ng/mL of nalmefene were considered therapeutic. The short half-life of the drug (2 to 3 hours in dogs) may necessitate frequent dosing.

Multiple-Animal Households

Abnormal behaviors that may accompany the addition of a new pet to the household that already has one or more pets (generally dogs) include excessive barking, territorial defense, predatory aggression (exhibited in dogs allowed to roam unsupervised), or intraspecies aggression (aggression toward other dogs either within or outside the household). Drugs that modify anxiety or fearfulness should be considered as adjuvant therapy. Included are the TCAs amitriptyline (Juarbe-Diaz, 1997a) and clomipramine (fear or anxiety), the SSRIs fluoxetine and paroxetine, the azapirone buspirone (antianxiety), and progestins. Of these drugs, fluoxetine and clomipramine may be most preferred. Amitriptyline and buspirone in particular have been cited for a potential increase in aggressive tendencies (Juarbe-Diaz, 1997a) with interdog aggression. Care should be taken to adhere to previously stated concerns regarding progestin therapy.

Excessive Barking

Occasionally, excessive barking reflects an OCD. Most cases are conducive to behavioral modification. Surgical treatment (vocal cordectomy) is a less desirable, yet alternative treatment. The use of behavior-modifying drugs should be reserved for cases in which fear, separation anxiety, or other compulsive component can be identified in association with the behavior (Juarbe-Diaz, 1997b). Drugs should be administered short term, 2 to 4 months, and in conjunction with behavior modification. Once the desirable behavior is achieved and maintained for 4 to 6 weeks, medication can be tapered gradually until it is discontinued. Occasional cases may require life-long medication in conjunction with behavioral modification. Drugs recommended by animal behaviorists include clomipramine, amitriptyline, buspirone, and fluoxetine (Juarbe-Diaz, 1997b). Thioridazine was reported useful in one case of excessive barking accompanied by tail biting (Jones, 1987).

Destructive Behavior

Destructive behavior can be dangerous to the animal (due to ingestion of foreign or toxic material) and economically undesirable to the pet owner. Causes of the behavior may vary with age. The underlying cause of the behavior may reflect exploration and play, attention-seeking, or expression of territory, fear, or separation anxiety. Cognitive dysfunction in geriatric animals also may be manifested as destructive behavior (Lindell, 1997). Although behavioral modification is an important component of therapy, drug therapy may be urgent for animals in whom the behavior is potentially harmful and for animals whose owners are intolerant of continued manifestation of the behavior.

Tranquilizers such as the phenothiazine derivatives (acepromazine) may appear appropriate for destructive behavior and occasionally might prove useful. Sedative effects may however, cause the animal to sleep rather than interact with family members (Lindell, 1997). Likewise, use of anxiolytics (e.g., clorazepate, diazepam) can cause sedation. Although rapid acting, the anxiolytics need to be administered frequently. In addition, they may interfere with the learning ability of the animal undergoing behavior modification (Lindell, 1997). Buspirone has proved poorly efficacious in many cases. In addition, it is characterized by a slow onset of action and is costly. Its safety may, however, warrant its use in some cases (Lindell, 1997). For animals whose destructive behavior reflects separation anxiety, a TCA (amitriptyline, clomipramine) or SSRI (fluoxetine) is indicated. As with buspirone, a long onset of action time and relatively high cost should be anticipated.

Anxieties, Noise Phobias

A common complaint of pet owners is that dogs exhibit disruptive behavior when left alone (Voith and Borchelt, 1985a). Behaviors include urination, defecation, barking, howling, chewing, and digging. Separation anxiety appears to respond well to fluoxetine; one open study reported 100% response rate (Melman, 1995). Benzodiazepines also may be effective for treatment of anxiety. Examples include chlordiazepoxide or diazepam (Beaver, 1992). An advantage of the latter group is rapid response.

Fear behaviors in dogs are also common (Voith and Borchelt, 1985b). Fear is commonly manifested toward loud noises such as thunderstorms and firecrackers, sudden movements, unfamiliar people, or novel environment. Before the advent of specific anxiolytic or antidepressant medications, tranquilizers such as phenothiazines or anticonvulsants such as phenobarbital were recommended for pharmacologic management of fear behaviors in dogs (Voith and Borchelt, 1985b). The efficacy of phenothiazine tranquilizers, however, reflects reduction of general responsiveness and is only likely for episodic anxieties (Simpson and Simpson, 1996). Benzodiazepines (including diazepam, clorazepate, and other derivatives) have stood the test of time for treatment of noise phobias (Voith and Borchelt, 1985b; Dodman and Shuster, 1994). They have been used to treat thunderstorm or other noise phobias. They must, however, be administered before the inciting event. For thunderstorm phobias, oral administration should occur at or before the first atmospheric sign (Overall, 1997), such as changes in atmospheric pressure or ambient light conditions. Clorazepate (sustained-release form) may be preferred to diazepam in order to avoid frequent administration. Alprazolam, characterized by a longer half-life, may also prove more beneficial (Overall, 1997). Dodman and Shuster (1994) reported that phobias can be palliatively treated, but not eradicated, with buspirone. Onset of action may, however, take up to 4 weeks.

Sexual Behaviors

Abnormal sexual behaviors are unusual. Both too "much" and too "little" behavior will benefit from a full reproductive workup, including serum sex steroidal hormone measurements. Behaviors that reflect "too much" generally are those targeted for behavioral modification, which might include drug therapy. Sexual behaviors that might be considered abnormal in uncastrated male dogs include house soiling and possessive or dominance aggression. Care must be taken to distinguish soiling from marking. Castration is the preferred treatment. Abnormal behaviors of castrated dogs include mounting, which may be accompanied by aggression, destructiveness, house soiling, and barking (Houpt, 1997a,b). Previous discussions regarding these behaviors apply when the behavior is a manifestation of sexual behavior.

Psychogenic Dermatoses

Psychogenic dermatoses generally consist of both a dermatologic and behavioral component. Discriminating between the two components is difficult but vital to successful therapy. Some psychogenic dermatosis will respond only to behavioral management, others only to dermatologic management, and some will require both behavioral and dermatologic therapy (Shanley and Overall, 1992). Dermatoses requiring medical management are discussed more in depth elsewhere (see Chapter 33).

Clinical manifestations of psychogenic dermatoses include pruritus, acral lick dermatitis and OCD disorders (e.g., trichotillomania), and self-mutilation manifestations (see previous discussion of OCD). Causes of psychogenic dermatoses are complex and may include boredom, endogenous opioid release (previously discussed), attention seeking, and, less commonly, separation anxiety (Shanley and Overall, 1992).

A number of drugs have been recommended for treatment of psychogenic dermatoses (Shanley and Overall, 1992). These include antihistamines such as hydroxyzine

sion in cats. Benzodiazepines have been used with variable results. Chlordiazepoxide or diazepam has been recommended for frustration or social anxiety in cats (Beaver, 1992; Marder, 1991; Voith, 1992). Diazepam may, however, increase predatory behavior in cats (Simpson and Simpson, 1996).

Psychogenic Dermatoses

Feline psychogenic alopecia presents as a traumatically induced regional alopecia. Underlying dermatologic causes include flea allergy, food allergy, and allergic inhalant dermatitis. Neurodermatitis also includes evidence of more damage (excoriations, crusting) and is more common in high strung cats such as Siamese, Burmese, and Abyssinian. The lesions reflect overzealous grooming. Recommended treatments include TCAs (clomipramine and amitriptyline) or antihistamines (Shanley and Overall, 1992). Fluoxetine was successful in a report of a single cat (Hartman, 1995).

Sexual Behaviors

Abnormal sexual behaviors in cats that may require management generally occur in toms and include urine spraying and mounting. Spraying by uncastrated cats is more appropriately treated by environmental management or according to previous discussions regarding inappropriate elimination; mounting that has not responded to behavioral modification techniques may respond to amitriptyline or another TCA (Houpt, 1997a,b).

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Muscle Relaxants 26

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INTRODUCTION
NEUROMUSCULAR BLOCKING AGENTS
Anatomy and Physiology of the Neuromuscular Junction
Pharmacology
Individual Agents
  Depolarizing Agents: Succinylcholine
  Nondepolarizing Agents
  Drug Interactions
Monitoring Neuromuscular Blockade
  Sites of Stimulation
  Electrical Stimulus Characteristics
  Patterns of Stimulation
  Quantifying Evoked Responses
Reversal of Neuromuscular Blockade
CENTRALLY ACTING SKELETAL MUSCLE RELAXANTS (SPASMOLYTICS)
Physiology
Pharmacology
Individual Agents
PERIPHERALLY ACTING SKELETAL MUSCLE RELAXANTS

INTRODUCTION

Skeletal muscle relaxants used in small animal practice include agents in three categories: neuromuscular blocking agents, centrally acting skeletal muscle relaxants, and peripherally acting skeletal muscle relaxants. Because their pharmacology and clinical indications differ, each category is presented separately.

NEUROMUSCULAR BLOCKING AGENTS

Anatomy and Physiology of the Neuromuscular Junction

The anatomic components of the skeletal neuromuscular junction include the somatic motor nerve terminal, synaptic cleft, and postsynaptic membrane of the muscle fiber, or motor endplate. The cell bodies of the somatic motor neurons are located within the spinal cord. The axon divides into multiple branches, each of which innervates a single muscle fiber in mammalian species. In birds, an individual muscle fiber is innervated by multiple axonal branches. This difference becomes important when considering the pharmacologic actions of certain neuromuscular blocking agents. At each neuromuscular junction the terminal portion of the axon loses its myelin sheath and forms an arborization that lies in close proximity to the specialized surface of the postsynaptic muscle membrane (Fig. 26–1). The nicotinic cholinergic receptors located at the postsynaptic membrane of the muscle fiber are the sites of action for neuromuscular blocking drugs.

Acetylcholine (ACh) is the endogenous neurotransmitter at the neuromuscular junction. Acetylcholine synthesis involves the acetylation of choline by the enzyme choline acetyltransferase, utilizing acetyl coenzyme A as the source of acetyl groups. Acetylcholine is then packaged at high concentrations into synaptic vesicles via carrier-mediated transport. When a motor nerve is stimulated and the action potential subsequently generated reaches the nerve terminal, ACh is rapidly released into the synaptic cleft via calcium-mediated exocytosis; one presynaptic nerve impulse releases 100 to 500 vesicles or approximately 3 million ACh molecules. Acetylcholine then diffuses across the synaptic cleft and, upon binding with a nicotinic cholinergic receptor, stimulates opening of an ion channel located on the muscle fiber membrane, allowing sodium ions to move into the muscle and potassium ions to move out. After a minimum number of ion channels open and allow sufficient current through them, the resting membrane potential is shifted toward threshold, generating an action potential that triggers muscle contraction. Unbound ACh within the synaptic cleft is rapidly hydrolyzed by the enzyme acetylcholinesterase to choline and acetate. The choline is taken up by the nerve terminal and recycled for continued synthesis of ACh (this is the rate-limiting step in ACh synthesis).

Pharmacology

Neuromuscular blocking agents exert their effects by interfering with the postsynaptic action of ACh and can be divided into two classes: nondepolarizing neuromuscular blocking drugs and depolarizing neuromuscular blocking drugs. Nondepolarizing neuromuscular blocking drugs elicit their pharmacologic effect by preventing ACh from binding to its receptors on the motor endplate (i.e., act as competitive antagonists). Consequently, the ion channels will not open, no shift in the resting membrane potential will occur, the motor endplate will not depolarize, and the muscle will become flaccid. Complete neuromuscular block requires approximately 90% to 95% receptor occupancy (Hunter, 1995).

Depolarizing neuromuscular blocking agents elicit their pharmacologic effect by binding to the ACh receptor in the same way that ACh does, causing an initial muscle fasciculation. Because these drugs are not immediately metabolized by acetylcholinesterase, however, they bind

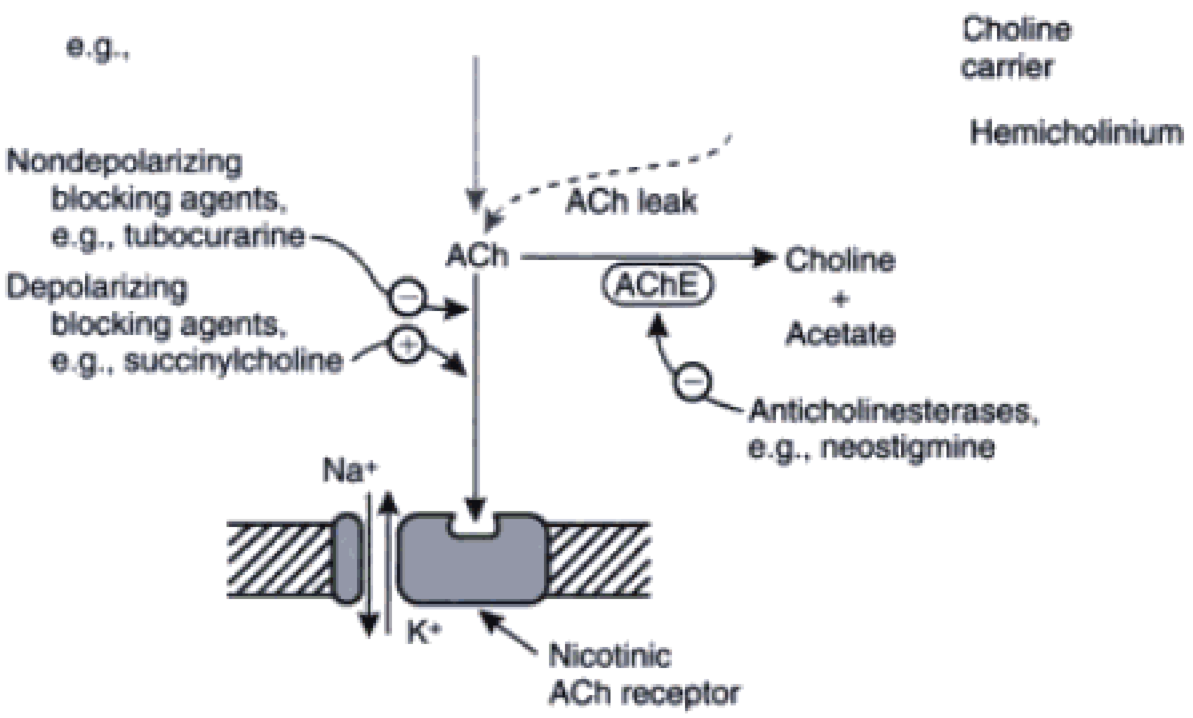
e.g.,
Choline carrier
Hemicholinium
Nondepolarizing blocking agents, e.g., tubocurarine
ACh leak
ACh
Choline + Acetate
AChE
Depolarizing blocking agents, e.g., succinylcholine
Anticholinesterases, e.g., neostigmine
Na+
K+
Nicotinic ACh receptor

Figure 26–1. Neuromuscular junction with sites of drug action. AcCoA = acetyl coenzyme A; ACh = acetylcholine; AChE = acetylcholinesterase; CAT = catecholamine; CoA = coenzyme A. (Reprinted by permission of the publishers from Rang HP, Dale MM, Ritter JM, et al: Pharmacology. New York, Churchill Livingstone, 1995.)

for a much longer period than ACh does, causing a persistent depolarization of the muscle fiber endplate. In mammals, the result of this maintained depolarization is a loss of electrical excitability by the postsynaptic muscle fiber, and subsequently a neuromuscular block occurs. In birds, because each muscle fiber is innervated by multiple axonal branches, a sustained, extensor spasm occurs. For this reason, the use of depolarizing neuromuscular blocking drugs (even topically on the eye) is contraindicated in birds.

Individual Agents

Neuromuscular blocking agents are given to anesthetized patients for several reasons. Because of their muscle relaxing effects, they are used during certain surgical procedures. Orthopedic procedures such as dislocation and fracture reductions can be performed more easily due to abolished skeletal muscle tone (Hall and Clarke, 1983). When a balanced anesthesia technique is used that combines opioids, nitrous oxide, and low-dose inhalant agents, muscle relaxation is greatly improved if a neuromuscular blocking agent is given. This technique is especially beneficial for critically ill patients in which high doses of inhalant agents may lead to unwanted cardiovascular depression (Ilkiw, 1992). During intraocular procedures or for patients with penetrating eye injuries requiring surgery, neuromuscular blocking agents can be beneficial by causing a central pupil, still eye, and soft globe. When used during induction and intubation, they can help prevent increases in intraocular pressure that can occur during coughing or vomiting (Ilkiw, 1992). When neuromuscular blocking agents are used, ventilation must be controlled and an adequate level of unconsciousness and analgesia must be present because this class of drugs can produce apnea and possesses no analgesic properties. Doses for depolarizing and nondepolarizing neuromuscular blocking agents for dogs and cats are listed in Table 26–1.

Depolarizing Agents: Succinylcholine

Succinylcholine is the only depolarizing neuromuscular blocking agent in clinical use today. Succinylcholine has a rapid onset of action, and its short duration of action is primarily due to rapid hydrolysis by plasma cholinesterase (Benson and Thurmon, 1980). For these reasons, succinylcholine is used routinely in human patients during anesthe-

Table 26–1. Doses of Neuromuscular Blocking Agents for Dogs and Cats

Drug	Dose (mg/kg IV)
Succinylcholine*	0.22 (dog) 0.11 (cat)
Atracurium*	0.22
Vecuronium*	0.1
Pancuronium*	0.044–0.11
Mivacurium	ND
Rocuronium†	0.18
Doxacurium‡	0.008

Abbreviation: ND = not determined in dogs or cats.
*Plumb (1985).
†Cason et al. (1990).
‡Savarese et al. (1987).

sia induction to facilitate endotracheal intubation. Its use in small animal patients has been limited because the larynx of the dog and cat is easily visualized and does not routinely exhibit excessive laryngospasm, making paralysis unnecessary for intubation (Hubbell, 1992).

Because of succinylcholine's short duration of action, frequent redosing or a constant infusion is needed for long-term paralysis. This may lead to tachyphylaxis (increased dose requirement) and change the character of the initial block (phase I block) to one similar to that with nondepolarizing agents (phase II block), which may prolong recovery time and require the use of a reversal agent (anticholinesterase therapy) (Silverman and Donati, 1994).

Succinylcholine has significant side effects. A transient increase in serum potassium concentration occurs due to leakage of potassium from the interior of cells. Severe, life-threatening hyperkalemia can occur after succinylcholine administration in patients with severe burns, trauma, nerve damage, neuromuscular disease, closed head injury, intra-abdominal infections, and renal failure (Miller and Savarese, 1986). Succinylcholine should also be avoided in patients in which increases in intraocular, intracranial, and intragastric pressures are undesirable. Other side effects include myalgia and cardiac arrhythmias (e.g., sinus bradycardia, catecholamine-induced ventricular arrhythmias) (Miller and Savarese, 1986).

Any agent that inhibits plasma cholinesterase (organophosphates, procaine) will prolong the duration of action of succinylcholine. Certain disease states such as liver disease, malnutrition, and chronic anemia can decrease the plasma cholinesterase level. Succinylcholine must be used cautiously, if at all, in these patients (Benson and Thurmon, 1980).

Several pharmaceutical companies have focused research and development on alternate nondepolarizing agents with a rapid onset of action and minimal side effects. To date, two agents are clinically available: rocuronium and mivacurium. Both are discussed in detail later in this chapter.

Nondepolarizing Agents

Atracurium Besylate Atracurium is an intermediate-acting nondepolarizing agent with an onset of action of 3 to 5 minutes and a duration of action of 20 to 35 minutes (Plumb, 1991). It is metabolized primarily through Hofmann elimination and ester hydrolysis (Fisher et al., 1986). For this reason atracurium is the muscle relaxant of choice for patients with hepatic or renal disease. The rate of spontaneous degradation via Hofmann elimination is pH and temperature dependent. Both acidemia and hypothermia prolong atracurium-induced neuromuscular blockade. Administration of atracurium can cause histamine release at higher doses, resulting in hypotension and tachycardia. Atracurium should be avoided in patients in which cardiovascular stability is desired.

Slow administration of large doses will attenuate these effects (Scott et al., 1985). Repeated doses or an infusion of atracurium produces a consistent degree of block and duration of action due to its noncumulative effects, making it an attractive choice for a constant rate infusion for long-term paralysis (Hildebrand, 1992; Miller et al. 1984). A metabolite of atracurium, laudanosine, can cause central nervous system (CNS) stimulation and cardiovascular depression, but this problem is rarely seen after use of clinical doses (Miller et al., 1984).

Vecuronium Bromide Vecuronium is an intermediate-acting nondepolarizing agent with an onset of action of 4 to 8 minutes and a duration of action of 20 to 30 minutes (Plumb, 1991). It has the advantage of a lack of cardiovascular or histamine-releasing effects, even at higher doses (Miller et al., 1984). Vecuronium is the muscle relaxant of choice when hemodynamic stability is needed. Recovery from vecuronium-induced muscle relaxation depends on hepatic elimination. Animals with hepatic disease may exhibit a prolonged duration of action. Vecuronium is noncumulative and is well suited for repeated doses or constant rate infusions (Miller et al., 1984).

Pancuronium Bromide Pancuronium is a long-acting nondepolarizing agent with an onset of action of 2 to 3 minutes and a duration of action of 40 to 45 minutes (Plumb, 1991). It lacks histamine-releasing effects but does possess vagolytic and sympathomimetic effects that can result in tachycardia, increased arterial blood pressure, and catecholamine-induced ventricular arrhythmias (Stoelting, 1972). Pancuronium is mainly eliminated by the kidney, with the remainder undergoing hepatic metabolism (Silverman and Mirakhur, 1994), and should therefore be used with caution in patients with renal or hepatic disease. Pancuronium is cumulative in repeated doses or infusions, which can produce a delayed recovery (Hildebrand, 1990).

Mivacurium Chloride Mivacurium was recently developed as an alternative to succinylcholine for intubation in human patients. Its onset of action is 1 to 2 minutes, with a duration of action of 15 to 20 minutes (Mirakhur, 1992). Because its metabolism is via plasma cholinesterase, prolonged recoveries are possible in patients with hepatic disease, renal disease, or organophosphate toxicity (Basta, 1992). Mivacurium can cause histamine release, is noncumulative, and can be used for infusion administration (Mirakhur, 1992). In human patients, the onset and depth of blockade have a high interpatient variability. Limited data are available regarding its use in small animal patients. Preliminary work in dogs suggests that the dose should be reduced below that given to human patients (Lukasik, 1996).

Rocuronium Bromide Like mivacurium, rocuronium was developed as a possible alternative to succinylcholine for intubation in human patients due to its rapid onset of action. In halothane-anesthetized dogs, rocuronium had an onset and duration of action of 1.1 ± 0.49 and 13.7 ± 0.49 minutes, respectively (Cason et al., 1990). Rocuronium lacks significant cardiovascular and histamine-releasing effects. It is metabolized primarily by the liver (Mirakhur, 1992). Its role in small animal anesthesia is unknown, but it may be helpful when a rapid onset of action without significant hemodynamic effects is desired.

Doxacurium Chloride Doxacurium is the most potent nondepolarizing agent available at this time (Mirakhur, 1992). It is a long-acting muscle relaxant with a slow onset of action and a long duration of action in human patients. Doxacurium has minimal cardiovascular or histamine-releasing effects (Faulds and Clissold, 1991). Metabolism is via renal elimination; therefore, a prolonged or more variable duration of action occurs in patients with renal disease (Cook et al., 1991). Doxacurium is not used currently in veterinary medicine. Due to its long duration of action, doxacurium may not be suitable for routine clinical use in small animal patients, but it may be an attractive choice for researchers when long-term relaxation with minimal hemodynamic effects is desired.

Drug Interactions

Many medications that are given to veterinary patients during the perioperative period can alter the pharmacodynamics and pharmacokinetics of nondepolarizing agents, leading to an increased or decreased effect. Table 26–2 lists various medications and their effects on the muscle relaxant.

Monitoring Neuromuscular Blockade

Whenever a muscle relaxant is administered, the neuromuscular junction should be monitored to allow the proper dose of relaxant and antagonist to be determined accurately. Also, the degree of residual blockade during the recovery period, if any, can be detected and treated appropriately. Evoked responses are used to evaluate neuromuscular blockade. This involves stimulating a peripheral nerve to evaluate the resultant motor response. Several hand-held peripheral nerve stimulators are available (Fig. 26–2).

Table 26–2. Effect of Medication on Nondepolarizing Neuromuscular Blockade

Drug	Effects on Depth/ Duration	Comments
Antibiotics	Increased	Calcium may reverse effect
Aminoglycosides		
Lincomycin		
Clindamycin		
Tetracycline		
Polymixins		Neostigmine will augment block
Anticholinesterases	Decreased	
Anticonvulsants	Increased	After chronic therapy (>2 weeks)
Phenytoin		
Carbamazepine		
Dantrolene	Increased	
Induction agents	Increased	Dose-dependent potentiation
Thiopental		
Propofol		
Ketamine		
Inhalational anesthetics	Increased	
Sedatives/tranquilizers	Increased	
Benzodiazepines		
Chlorpromazine		
Steroids	Increased or decreased	Most likely decrease, but may also increase or exert no effect
Succinylcholine	Increased	When given before nondepolarizing agents
Theophylline	Decreased	

From Silverman DG, Mirakhur RK: Effects of other agents on nondepolarizing relaxants. In Silverman DG (ed): Neuromuscular Block in Perioperative and Intensive Care, pp 104–122. Philadelphia, JB Lippincott, 1994.

Sites of Stimulation

Sites for stimulation of peripheral motor nerves in dogs and cats include the peroneal and ulnar nerves. The most accessible is used (Fig. 26–3).

Electrical Stimulus Characteristics

There are standard methods of stimulating peripheral motor nerves because the physical characteristics of electrical stimuli influence the motor response they evoke. The output from the peripheral nerve stimulator should be a square wave stimulus having a duration of 0.2 to 0.3 ms. Ideally, the output current is adjustable and should be sufficient to produce a supramaximal impulse.

After the two electrodes are placed over the nerve to be stimulated, the stimulus is adjusted to deliver a supramaximal current, slightly greater than that required to elicit a maximum motor response. This ensures that all neurons in the bundle are depolarized, which will cause the muscle fibers to contract in an all-or-none fashion. Any subsequent changes in the motor response are from effects at the neuromuscular junction.

Patterns of Stimulation

Peripheral nerve stimulators should provide single twitch, tetanus of 50 Hz, and train-of-four stimulus patterns. Newer stimulators may also have the capability to deliver a double-burst pattern (Fig. 26–4).

Single Twitch The single twitch method is used to evaluate the degree of relaxation by dividing the elicited response by the control response. The control response is measured before the administration of the relaxant. The frequency should not be more than 0.15 Hz (one twitch/7–10 s). This is due to the prejunctional effects of the relaxant, which greatly decrease the amount of ACh release (Ali and Savarese, 1980). The resultant motor response will be less than the baseline value, making accurate determination of the degree of relaxant difficult. The disadvantages of the single twitch method are that it is necessary to have a baseline response before administration of the muscle relaxant and that the method is insensitive for the detection of residual blockade (Ali and Miller, 1986).

Train-of-Four The train-of-four method consists of four supramaximal impulses delivered at a frequency of 2 Hz (two twitches/s). The degree of blockade is evaluated by comparison of the ratio of the fourth twitch to the first twitch ($T_4T/_1$ ratio). The train-of-four serves as its own control; therefore, knowledge of the baseline value before muscle relaxant administration is not necessary. The train-of-four stimulus can be delivered intermittently or at regular intervals 10 to 20 seconds apart.

Table 26–3. Doses of Neuromuscular Reversal Agents for Dogs and Cats

Drug	Dose (mg/kg IV)
Neostigmine*	0.04
Edrophonium*	0.5
Pyridostigmine†	0.2

*Muir WW, Hubbell JAE, Skarda R: Neuromuscular blocking drugs. In Muir WW, Hubbell JAE (eds): Handbook of Veterinary Anesthesia: 108–117. St. Louis, CV Mosby, 1989.

†Dose used at Veterinary Teaching Hospital, Texas A&M University.

ally rapid and spontaneous due to rapid hydrolysis by plasma cholinesterases. Delayed recovery occurs in patients with decreased plasma cholinesterase levels.

Residual neuromuscular blockade from nondepolarizing agents and phase II block from succinylcholine are reversed at the conclusion of surgery to prevent potentially serious complications in the recovery period. These include muscle weakness and inadequate ventilation, which can lead to life-threatening hypoxia or respiratory acidosis.

Before reversal of blockade, it is desirable to have three to four twitches of the train-of-four visible. This is achieved by close monitoring of neuromuscular function throughout surgery and avoiding redosing the patient close to the time of anticipated reversal.

The anticholinesterase drugs used clinically include neostigmine, pyridostigmine, and edrophonium. Doses are listed in Table 26–3. They reverse neuromuscular blockade by inhibiting the enzyme acetylcholinesterase, which is responsible for the hydrolysis of ACh. The effect is an accumulation of ACh at muscarinic and nicotinic receptor sites. Because nondepolarizing agents and ACh compete for the same receptor binding sites, anything that increases the concentration of ACh tips the balance of competition in favor of ACh and restores neuromuscular transmission. Reversal of neuromuscular blockade requires only the nicotinic cholinergic effects of anticholinesterase drugs; therefore, the muscarinic effects are attenuated or prevented by concurrent administration of an anticholinergic agent such as atropine or glycopyrrolate.

Monitoring of neuromuscular function and support of ventilation must be continued until complete reversal has been accomplished. A light plane of anesthesia must be maintained while the degree of block is monitored with a peripheral nerve stimulator because this can cause the patient some discomfort, especially if tetanic stimulation is used. A T_4/T_1 ratio of 0.7 or greater correlates well with clinical recovery. Once reversal is complete and the use of the nerve stimulator is discontinued, the animal is allowed to recover from anesthesia. Although recurarization is uncommon after reversal, spontaneous respiratory efforts sufficient to maintain adequate ventilation should be present and monitored closely during the recovery period.

CENTRALLY ACTING SKELETAL MUSCLE RELAXANTS (SPASMOLYTICS)

Although skeletal muscle spasticity can be relaxed by neuromuscular blocking drugs, these drugs are too nonselective to be clinically useful for this purpose. A number of other agents are available that reduce muscle tone without completely inhibiting voluntary contraction of skeletal muscle. Side effects produced by these agents are primarily limited to CNS depression, commonly manifested as drowsiness.

Physiology

The pathophysiology of skeletal muscle spasticity is not completely understood, but it appears to involve dysfunction of descending spinal pathways that exert control over motor neurons. Hyperexcitability of tonic stretch reflexes, painful flexor spasms, and muscle weakness may all be characteristics of this type of disorder. Diseases involving increased muscle tone associated with defective neuronal control of muscle activity have been described in Scottish terriers (Scotty cramps), Dalmatians, and Labrador retrievers. Clinical signs frequently occur after exercise and may improve with administration of centrally acting muscle relaxants. Intervertebral disc disease in dogs may cause painful spasms of neck and shoulder (cervical disc) or back (thoracolumbar disc) muscles. In selected situations, skeletal muscle relaxants may be employed as part of a conservative management protocol for intervertebral disc disease.

Pharmacology

Centrally acting skeletal muscle relaxants have the effect of reducing muscle tone without abolishing voluntary motor control. The exact mechanism by which these drugs work is not completely understood but is thought to involve disruption of nerve impulse transmission at the internuncial neuron level of the spinal cord, brain stem, and subcortical areas of the brain. These drugs have little effect on the diaphragm and respiratory muscles at therapeutic doses.

Individual Agents

Centrally acting skeletal muscle relaxants used in small animal veterinary medicine include guaifenesin, methocarbamol (which is structurally related to guaifenesin), and the benzodiazepines (diazepam in particular). As stated earlier, the most frequently encountered side effect of these agents is CNS depression, which is manifested as sedation and lethargy. Other possible side effects include ataxia and muscle weakness. Diazepam may produce hepatic toxicity in cats after prolonged administration. Elimination of each of these drugs depends on hepatic metabolism. Because these drugs are CNS depressants, additive depression may occur when given with other CNS depressant agents. Metabolism of diazepam may be decreased and excessive sedation may occur if administered with cimetidine, erythromycin, ketoconazole, or propranolol. Anticholinesterase agents given concurrently with either guaifenesin or methocarbamol may result in severe muscle weakness.

The clinical indications for centrally acting skeletal muscle relaxants may be specific for the individual agent. For example, guaifenesin is used in veterinary medicine primarily to induce muscle relaxation as an adjunct to anesthesia at a dose of 33 to 88 mg/kg intravenously (IV) (dogs). Although guaifenesin has been recommended for the treatment of toxicoses (e.g., strychnine) and tetanus, diazepam and methocarbamol are more commonly used for this purpose.

Methocarbamol is labeled for adjunctive therapy of acute inflammatory and traumatic conditions of the skeletal muscle and to reduce muscular spasms in dogs and cats at a dose of 44 mg/kg IV or 61 to 132 mg/kg orally initially divided every 8 to 12 hours (dogs and cats). For muscle relaxation for intervertebral disc disease in dogs, methocarbamol is used at a dose of 15 to 20 mg/kg three times a day as part of a conservative management treatment program. Additional components of a conservative management program for intervertebral disc disease include strict cage confinement, attentive nursing care, and cautious use of anti-inflammatory drugs (Toombs, 1992; Jeffrey, 1995). The reader is encouraged to consult the aforementioned references for further information on conservative management of intervertebral disc disease. To control muscle spasms associated with tetanus or strychnine toxicosis in dogs or cats, methocarbamol is used at a dose of 50 to 200 mg/kg IV as needed.

The clinical indications for diazepam are diverse and include seizure control, appetite stimulation, tranquilization, and skeletal muscle relaxation. Only its use as a skeletal muscle relaxant is discussed here. As a component of a conservative management treatment program for disc disease in dogs, diazepam is used at a dose of 1.1 mg/kg two times daily (maximum of 20 mg/day). For treatment of muscle spasms associated with tetanus or strychnine toxicosis, diazepam may be administered at a dose of 2.5 to 5 mg IV total (cats) or 5 to 10 mg IV total (dogs), as needed. Diazepam may be effective in reducing skeletal muscle spasticity in dogs with episodic muscle cramping such as Scotty cramps or in certain myopathic syndromes (dose ranges from 0.5 to 2 mg/kg IV or PO three times a day).

Diazepam is also used to treat intraurethral obstruction secondary to acquired lower urinary tract disease in male cats. It is believed that muscle spasms of the urethra, along with inflammation of the urethral tissue, make removal of the obstructing plug more difficult. Additionally, these factors may create a "functional" obstruction of the urinary tract even after the obstructing plug has been removed. Diazepam has been recommended for treatment of external urethral sphincter hypertonus at a dose of 2 to 10 mg (total) every 8 hours. Because the urethral musculature contains a predominance of smooth muscle, skeletal muscle relaxants (which only affect the external urethral sphincter) may need to be combined with smooth muscle relaxants such as prazosin.

There are a number of agents used for therapy of skeletal muscle spasms in human patients. Little is known about their use in veterinary medicine. These agents include carisoprodol (Soma), metaxalone (Skelaxin), cyclobenzaprine (Flexeril), and baclofen (Lioresal).

PERIPHERALLY ACTING SKELETAL MUSCLE RELAXANTS

Dantrolene is the only clinically useful peripherally acting skeletal muscle relaxant drug in veterinary medicine. The pharmacologic effects of dantrolene are due to its ability to interfere with the release of calcium from the sarcoplasmic reticulum; however, it does not appear to affect cardiac muscle or the muscles of the respiratory system at usual therapeutic doses.

Dantrolene has moderate to poor oral bioavailability and is highly bound to albumin. Dantrolene undergoes hepatic metabolism with metabolites excreted in the urine. Adverse effects include hepatotoxicity (most significant; should be monitored for), sedation, muscle weakness, and gastrointestinal effects).

Clinical indications include functional urethral obstruction due to increased external urethral tone and treatment of malignant hyperthermia. For treatment of functional urethral obstruction, dantrolene is administered at a dose of 1 to 5 mg/kg PO every 8 hours (dogs) or 0.5 to 2 mg/kg every 8 hours (cats). Dantrolene has been shown to decrease intraurethral pressure in the postprostatic/penile urethral segment but has no effect on intraurethral pressures in the prostatic or preprostatic urethral segment (Straeter-Knowlen et al., 1995). Concurrent use of smooth muscle relaxants may be of benefit in relieving urethral obstruction. For treatment of malignant hyperthermia, dantrolene is administered at a dose of 1 mg/kg IV.

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27 Gastrointestinal Pharmacology

Dawn Merton Boothe

- APPETITE STIMULANTS
- EMETICS AND ANTIEMETICS
- The Vomiting Reflex
- Emetics
  - Peripherally Acting or Reflex Emetics
  - Centrally Acting Emetics
- Antiemetics
  - Centrally Acting Antiemetics
  - Peripherally Acting Antiemetics
- ANTI-ULCER DRUGS
- Pathophysiology of Gastrointestinal Ulceration
  - Gastroduodenal Ulceration
  - Physiology of Gastric Acid Secretion
  - Mucosal Defenses
  - Gastric Antisecretory Drugs
  - Cytoprotective Drugs
- MODULATORS OF GASTRIC MOTILITY
- Normal Physiology
- Receptors
- Prokinetics
  - Cholinergics
  - Metoclopramide
  - Domperidone
  - Cisapride
- DRUGS AFFECTING THE INTESTINAL TRACT
- Physiology, Pathophysiology, and Motility
- Modulators of Intestinal Motility and Secretions
  - Anticholinergic Agents
  - Opioids
  - Miscellaneous Antisecretory Drugs
- GASTROINTESTINAL PROTECTANTS AND ABSORBENTS
- LAXATIVES AND CATHARTICS
- Emollient Laxatives
- Simple Bulk Laxatives
- Osmotic Cathartics
- Irritant Cathartics
- Enemas
- DRUGS AFFECTING THE LIVER
- Cholagogues and Choleretics
- Liver Protectants and Hepatotropic Agents
  - Choline
  - Methionine
  - Lecithin
  - Selenium and Vitamin E
  - Vitamins
  - Hydroxocobalamin
  - Glucose and Fructose
- AGENTS PROMOTING DIGESTIVE FUNCTIONS
- Digestive Enzymes
- TREATMENT OF SPECIFIC DISORDERS OF THE GASTROINTESTINAL TRACT
- Diseases of the Oral Cavity
- Diseases of the Esophagus
- Diseases of the Stomach
  - Acute Gastritis
  - Gastric Ulceration/Erosion
  - Gastric Dilatation Volvulus
  - Gastric Motility Disorders
- Small Intestinal Diseases
  - Diarrhea
  - Viral Enteritis
  - Bacterial Enteritis
  - Hemorrhagic Gastroenteritis
  - Chronic Diarrhea
  - Short Bowel Syndrome
- Diseases of the Large Intestine
  - Diarrhea
- Inflammatory Bowel Disease
- Liver Diseases
  - Acute Hepatic Failure
  - Chronic Hepatic Diseases
  - Sequelae of Chronic Liver Disease
- Diseases of the Pancreas
  - Acute Pancreatitis
  - Exocrine Pancreatic Insufficiency

APPETITE STIMULANTS

Appetite is controlled primarily but not exclusively by the ventral and lateral nuclei of the hypothalamus (Sugrue, 1987). Several major neurotransmitters have been identified in the control of appetite (Sugrue, 1987). Stimulatory mediators include norepinephrine through α_2-receptors and dopamine (possibly through D_1 receptors), whereas serotonin (5-hydroxytriptamine [5-HT]) is inhibitory. γ-Aminobutyric acid (GABA) also stimulates appetite, although its effect is controversial and may vary with route of administration (Sugrue, 1987). Several neuropeptides have also been implicated in the control of appetite because of their ability to modulate neurotransmitter release. Opiate and pancreatic polypeptides are associated with increased appetite. Other neuropeptides such as calcitonin, cholecystokinin, and corticotrophin-releasing factor inhibit appetite (Sugrue, 1987).

Studies regarding the pharmacologic control of appetite have traditionally focused on decreased food intake in humans, whereas the need in veterinary medicine tends to be increased appetite. The role of cachexia associated with weight loss and anorexia in human cancer patients has stimulated a renewed interest in appetite stimulants (Spaulding, 1989). Drugs that inhibit gluconeogenesis, such as hydrazine sulfate, or promote gastric emptying, such as metoclopramide, have been used successfully to stimulate food intake in some patients (Spaulding, 1989). Megestrol acetate has caused appetite stimulation in human patients with advanced cancer and is preferred to anabolic steroids, which are associated with more adverse side effects (Spaulding, 1989). The side effects of megestrol acetate preclude its routine use as an appetite stimulant in small animals.

The benzodiazepines diazepam (Valium) and oxazepam, a metabolite of diazepam (Serax), have been used to successfully induce appetite in cats, probably through GABAminergic effects and central inhibition of the satiety center in the hypothalamus (Macy and Gasper, 1985) (Table 27–1). Diazepam is administered intravenously or orally, whereas oxazepam is administered orally. Of the two drugs, diazepam may be more effective, although sedation is greater. The benzodiazepines do not stimulate appetite in the dog as effectively as in the cat. Hepatotoxicity associated with diazepam therapy when used as an appetite stimulant has been reported in cats (Center et al., 1996; Hughes et al., 1997). The toxicity appears to be idiosyncratic and thus may not be predictable and is not likely to happen in a large percentage of animals receiving the drug.

Cyproheptadine, an antihistamine with antiserotonin properties, has caused weight gain in geriatric human patients and adults and younger patients afflicted with eating disorders. Its mechanism probably reflects inhibition of serotoninergic receptors that control appetite. Serotonin antagonists also increase food intake in cats (Sugrue, 1987), and, clinically, cyproheptadine has been used to stimulate the appetite of some anorexic cats. Cyproheptadine kinetics have been reported in the cat. Oral bioavailability of the tablet is 100%, and the elimination half-life approximates 13 hours (Norris et al., 1998). Cats tolerated a dose of 8 mg orally with no adverse effects. Based on this study, once to twice daily dosing of 8 mg appears to be safe. Both glucocorticoids and B vitamins have been used to nonspecifically stimulate an animal's appetite. Drugs used to treat depression and psychosis in human patients are associated with appetite increase and weight gain (Bernstein, 1988). They antagonize a variety of receptors, although their clinical potency is often related to increased serotonin, which may, in fact, decrease appetite in some patients.

EMETICS AND ANTIEMETICS

The Vomiting Reflex

Emesis is a complex, protective reflex that is not well developed in all species but does occur in carnivores (Johnson, 1984, 1985; Andrews et al., 1988). Drugs that cause or ameliorate vomiting generally do so by modifying neurotransmitters responsible for transmission of the signal from various sites. Drug penetrability to each site varies, complicating effective emetic and antiemetic therapy. Emesis is controlled through the emetic center located in the lateral reticular formation of the medulla; as such, at this site, the center is protected by the blood-brain barrier (Fig. 27–1) (Johnson, 1984, 1985; Andrews et al., 1988; Merrifield and Chaffee, 1989).

Although several afferent pathways may be responsible for initiating emesis, all signals are coordinated by the emetic center. Impulses to the emetic center in the medulla may arise from higher centers such as the cerebral cortex and limbic system. Psychogenic vomiting and that arising from visual and olfactory stimuli originate in the cerebral cortex, whereas head injuries and increased intracranial pressure initiate emesis via limbic pathways. Acetylcholine is the primary afferent neurotransmitter that mediates emesis from these higher centers, although histamine acts as a secondary transmitter via H_1 receptors (Merrifield and Chaffee, 1989). Blood-borne chemical compounds may stimulate the chemoreceptor triggering zone (CRTZ), which is located in the area postrema in the lateral walls of the third ventricle (Johnson, 1985; Merrifield and Chaffee, 1989). This area does not possess a complete blood-brain barrier, so it is more readily accessible than the emetic center to substances such as drugs or toxins present in circulating blood. The neurons of the CRTZ are also more responsive to the presence of blood-borne and cerebrospinal fluid (CSF)-borne chemical compounds because free nerve endings directly contact the CSF. Emesis caused by blood-borne mediators (e.g., uremia, pyometra, liver disease, endotoxemia, and those associated with radiation sickness disease) and drugs (e.g., digitalis glycosides, apomorphine, narcotic analgesics, and estrogens) is mediated by the CRTZ.

Stimulation of the CRTZ is initiated by dopaminergic (D_2) receptors that respond to agonists such as dopamine and apomorphine (Merrifield and Chaffee, 1989). Serotonin (5-hydroxytryptamine [5-HT_3]) also appears to be an important mediator of emesis in this area (Kohler and Goldspiel, 1991). Histamine via H_1 receptors acts as a secondary neurotransmitter at the CRTZ. As with dopaminergic receptors, H_1 receptors may also be competitively and noncompetitively inhibited by antagonists. Clinical efficacy of drugs active in the CRTZ may reflect selectivity for subreceptor types for each neurotransmitter. At least five dopamine, nine serotonin, and five histamine subreceptors have been identified; which of each subreceptor type is affected by each drug is not always known. α_2-receptors and $5HT_3$ associated with the area postrema also induce emesis in dogs and other species (Brunton, 1995b; Hikasa et al., 1992) and cats (Hikasa et al., 1989).

Impulses originating from the semicircular canals of the vestibular apparatus are transmitted by the eighth cranial nerve to the vestibular nuclei, and then via the CRTZ and the uvula and nodulus of the cerebellum, to the emetic center. This pathway, mediated by histaminergic (subtype H_1) receptors, is responsible for eliciting the emesis that accompanies motion sickness and labyrinthitis (Peroutka and Snyder, 1982).

Peripheral impulses causing vomiting that arise from stimulation of the pharynx and fauces are transmitted by afferent nerves in the ninth cranial nerve to the emetic center. Other peripheral afferent pathways include those arising from stimulation (i.e., irritation or distension) of various visceral organs and tissues. Impulses may be carried by sympathetic or vagal afferents from the heart, stomach, duodenum, small intestine, liver, gallbladder, peritoneum, kidneys, ureter, urinary bladder, and uterus. Acetylcholine is the primary neurotransmitter mediating the afferent limb of the emesis reflex from peripheral causes. Muscarinic receptors initiate the impulse that travels to the emetic center via the vagus nerve. Efferent signals that stimulate the emetic reflex travel back to the stomach by the tenth cranial (vagus) nerve. Acetylcholine also acts as the primary efferent neurotransmitter in the vagus and in the smooth muscle of the stomach. In the stomach, dopamine receptors appear to inhibit gastric motility during nausea and vomiting. In addition, dopamine receptors contribute to reflexes that allow relaxation of the upper stomach and delayed gastric emptying associated with gastric distension caused by food (Brunton, 1995b). Serotonin (via 5-HT_3 receptors) is emerging as an important neurotransmitter in the emetic reflex. It serves in the afferent pathways from the stomach and small intestine (Brunton, 1995b).

Emetics

Clinically, emesis is pharmacologically induced in order to empty the anterior portion of the digestive tract. Indications include induction of general anesthesia if there is any

Table 27–1. Doses of Drugs Used To Treat Gastrointestinal Disorders

	Dose	Route	Interval
Activated charcoal	1–4 g/kg	PO as slurry	As needed (1 g/5 mL H_2O)
	6–10 mL/kg	Suspension PO	As needed
Aluminum hydroxide	100–200 mg (D)	PO	4–6 h
	50–100 mg (C)	PO	4–6 h
	0.5 mL/kg (C)	PO	4–6 h
Apomorphine	0.04 mg/kg (D)	IV	
	0.07 mg/kg (D)	IM	
	0.25 mg/kg (D)	PO*	As needed
Ascorbic acid	25–125 mg/kg (C)		
Copper toxicity	100–500 mg (D)	PO	24 h
Acetaminophen toxicity	30 mg/kg (C)	PO, SC	6–7 treatments
Atropine	0.02 mg/kg	SC	As needed
Bisacodyl	5–20 mg (D)	PO	24 h, as needed
	5–5 mg (C)	PO	24 h, as needed
Bismuth subsalicylate	10–30 mL (D)	PO	4–6 h
	0.25–2 mL/kg (D)	PO	6–8 h
	1–3 mL/kg (C)	PO	4–6 h
Calcium carbonate	0.5–4 g (D)		
Chlorpromazine	0.05–4.4 mg/kg (D)	IV	6–8 h
	0.25–0.5 mg/kg (D)	SC, IM	6–8 h
	3.3 mg/kg (D)	PO	6–8 h
Choline	40–50 mg/kg (D)	PO	
	100 mg (C)		
Cholestyramine	200–300 mg/kg	PO	12 h, as needed
Cimetidine (D)	5–10 mg/kg/6–8 h	PO	
	10 mg/kg/6 h	IV†	
Cisapride	0.1–0.5 mg/kg (D)	PO	8–12 h
	2.5–5 mg/kg (C)	PO	8–12 h
Cyclizine hydrochloride	4 mg/kg (D)	IM	8 h
Cyproheptadine	1.1 mg/kg	PO	8–12 h
	1 mg/cat	PO	12–24 h
Danthron	300–400 mg (D)		
Dehydrocholic acid	100 mg/kg or 10–15 mg/kg	PO	Every 12 h
Diazepam	0.05–0.2 mg/kg (C)	IV	24 h, as needed
	1–2 mg/cat	PO	24 h, as needed
Dicyclomine hydrochloride	5–10 mg	PO	8 h
	0.15 mg/kg (D)	PO	8 h
Dioctyl sodium sulfosuccinate			
	25–120 mg (D)	PO	12–24 h
	15–30 mg (C)	PO	12–24 h
Diphenhydramine hydrochloride	2–5 mg/kg (D)	PO	6–8 h
Diphenoxylate hydrochloride	0.1–0.2 mg/kg (D)	PO	8–12 h
	0.05–0.1 (C)	PO	12 h
Domperidone	0.1–0.5 mg/kg (D)	IM, IV	12 h
	2–5 mg/kg (D)	PO	12 h
Edrophonium chloride	0.11–0.22 mg/kg (D)	IV	Provocative test
	0.25–0.5 mg (C) (up to 2.5 mg/cat)	IV	Provocative test
Famotidine	0.5–1.0 mg/kg (D)	PO, IV	12–24 h
Flumazenil	2–5 mg (0.1 mg/kg) (D)	IV	As needed
Glycopyrrolate	0.01–0.02 mg/kg	IV, IM	8 to 12 h, as needed
Hydrogen peroxide	5–10 mL	PO	As needed × 1–2
Isopropamide iodide	0.05–0.40 mg/kg (D)	PO	8–12 h
(0.1–1.2 mg/kg)	0.07/cat	PO	12 h
Kaolin pectin	1–2 mL	PO	2–6 h
Lactitol	500 mg/kg	PO	2 divided daily
Lactulose	15–30 mL/kg	PO	6 h
	2.5–5 mL (C)	PO	6 h
	5–10 mL diluted	Rectal	12 h
Lecithin	1–5 g		
Loperamide	0.08–0.20 mg/kg (D)	PO	8–12 h
	0.1–0.3 mg/kg (C)	PO	12–24 h
Magnesium hydroxide			
Antacid	5–30 mL (D)	PO	8–24 h
Antacid	5–10 mL (C)	PO	8–24 h
Cathartic	3–6 × above doses	PO	8–24 h
Magnesium sulfate	2–60 g (D)		
Meclizine hydrochloride	2–10 mg/kg up to 10 kg (D)	PO	24 h
	or 2–6 mg/kg over 10 kg (D)	PO	24 h
	4 mg/kg (C)	PO	24 h
	12.5 mg (C)	PO	24 h

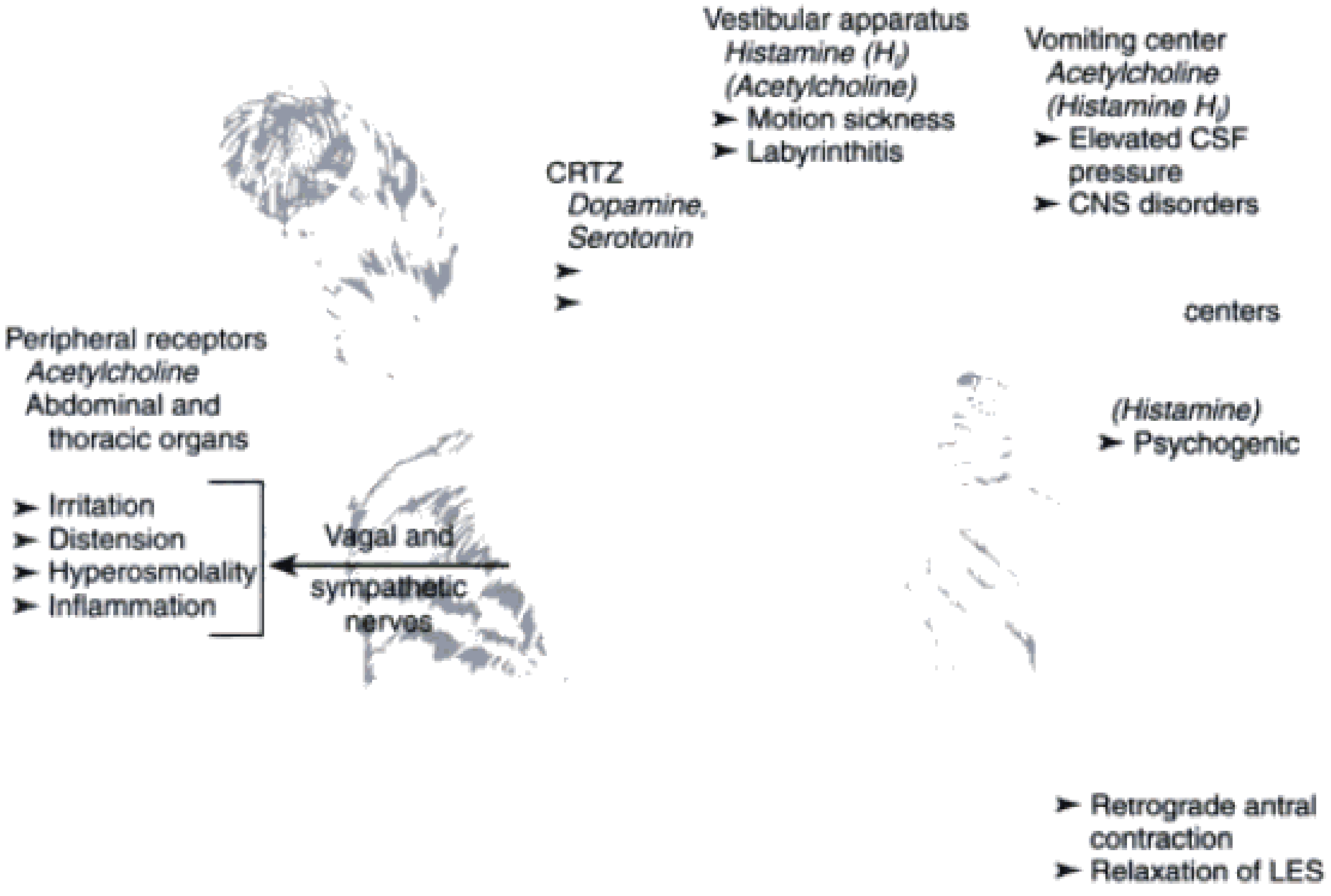

Figure 27–1. Sites that mediate the emetic reflex. The major neurotransmitter responsible for mediating the reflex at each site is noted in italics; secondary neurotransmitters at each site are in parentheses. Stimuli that mediate emesis at each site are listed below the neurotransmitter. CNS = central nervous system; CRTZ = chemoreceptor triggering zone; CSF = cerebrospinal fluid; LES = lower esophageal sphincter.

potentially toxic doses of the drug. Although ipecac syrup or powder has been used as an emetic for many years for cats, it has been known to induce toxic effects, including death.

Centrally Acting Emetics

Although a number of drugs are capable of stimulating the CRTZ centrally, certain opiates, particularly apomorphine, are the most commonly used. Apomorphine hydrochloride is a synthetic derivative of morphine with only marginal depressant activity. Its emetic activity predominates over other morphine-like actions and reflects stimulation of dopaminergic receptors in the CRTZ. Apomorphine can be administered by almost any route, although oral doses are higher in order to compensate for reduced oral bioavailability. Emesis generally occurs in 2 to 10 minutes after subcutaneous or conjunctival administration. Although apomorphine stimulates vomiting at the CRTZ, it also directly depresses the emetic center, and subsequent doses are even less likely to induce emesis if emesis does not occur after the first dose. Excessive doses of apomorphine can depress the central nervous system (CNS), particularly the respiratory center, and are contraindicated in the presence of existing central depression.

Apomorphine was withdrawn from the market in the late 1980s but subsequently returned. The commercial preparation may be prohibitively expensive. The drug might be acquired through a re-compounding pharmacy that has membership with Professional Compounding Companies of America (PCCA; 800-331-2498). Xylazine (Rompun) is an α_2-agonist used most commonly for its sedative analgesic properties. Emesis mediated by α_2 stimulation can, however, occur in cats when administered below doses recommended for sedation (0.05 mg/kg) (Hikasa et al., 1989). Emesis in dogs is not as consistent as in cats. The use of medetomidine to induce emesis has not been reported, although its actions are similar to those of xylazine.

Antiemetics

Antiemetics control emesis by either a central or a peripheral action (Fig. 27–2). Both actions depend on and can be correlated with blockade of neurotransmission at receptor sites (Peroutka and Snyder, 1982; Costall and Naylor, 1992). Centrally acting antiemetics block impulses at higher centers and at the emetic center and include muscarinic anticholinergics; antidopaminergics, which block dopaminergic receptors at the CRTZ; and antihistaminergics, which block H_1 receptors at the vestibular apparatus and secondarily at the CRTZ and the emetic center. Antiemetic agents possess either a limited or a broad effect, depending on which centers are depressed.

Centrally Acting Antiemetics

Vestibular Apparatus

Vomiting caused by motion sickness or inner ear disease is mediated by the vestibular apparatus. Motion sickness in dogs and cats can be controlled for several (8 to 12) hours by administration of antihistaminics such as cyclizine hydrochloride, meclizine hydrochloride, or diphenhydramine hydrochloride (Fig. 27–3). Although efficacy depends on a direct effect on neural pathways arising in the vestibular apparatus, actions may actually be independent of antihistaminic or sedative potencies. Emesis produced by other stimuli is not controlled by these drugs. Drowsiness and xerostomia (dry mouth) are typical side effects that occur with use of this group of drugs.

Selected antimuscarinic agents are used to control motion sickness in dogs. The belladonna alkaloids, especially hyoscine (scopolamine) and synthetic compounds such as

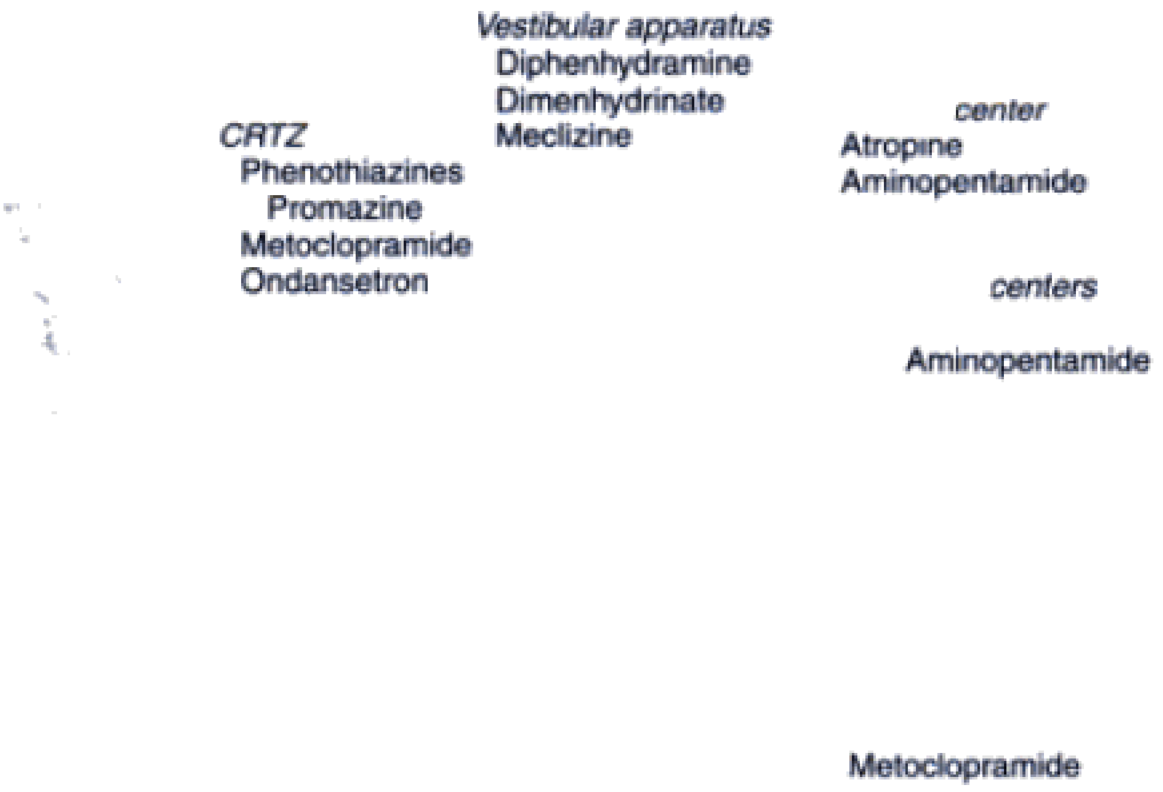

Figure 27–2. Antiemetic drugs effective at each site of the emetic reflex. CRTZ = chemoreceptor triggering zone.

dicyclomine hydrochloride and isopropamide iodide, are effective antiemetics. Their duration of action is short (up to 6 hours), and xerostomia, drowsiness, and other side effects may be anticipated. These drugs are not generally used for cats, probably because of potential adverse reactions.

Drugs Active at the Chemoreceptor Triggering Zone

Phenothiazines Phenothiazines are broad-spectrum antiemetics that control emesis induced by most central causes other than labyrinthine stimulation (see Fig. 27–3). Phenothiazines block emesis mediated by the CRTZ at low doses because of their antidopaminergic (D_2) and antihistaminergic effects. At higher (perhaps nonpharmacologic) doses, their anticholinergic effects may also act at other central sites, including the vomiting center. A variety of phenothiazine derivatives (e.g., chlorpromazine, prochlorperazine, triflupromazine, perphenazine, trifluoperazine, and mepazine) are used in small animals as antiemetics. The primary adverse effects associated with their use as antiemetics are sedation and hypotension due to peripheral α-blockade. Selection of a particular phenothiazine may be based on avoidance of adverse reactions. Fluid replacement therapy should be instituted if necessary before use of a phenothiazine. Phenothiazine derivatives should not be used in epileptic dogs because they lower the seizure threshold (see Chapter 25).

Butyrophenone Derivatives Haloperidol (Haldol) and droperidol (Inapsine), which are also used as major tranquilizers, are potent antiemetics because of their antidopaminergic activity. These drugs are rarely used as antiemetics because of their side effects (similar to those encountered with the phenothiazine group).

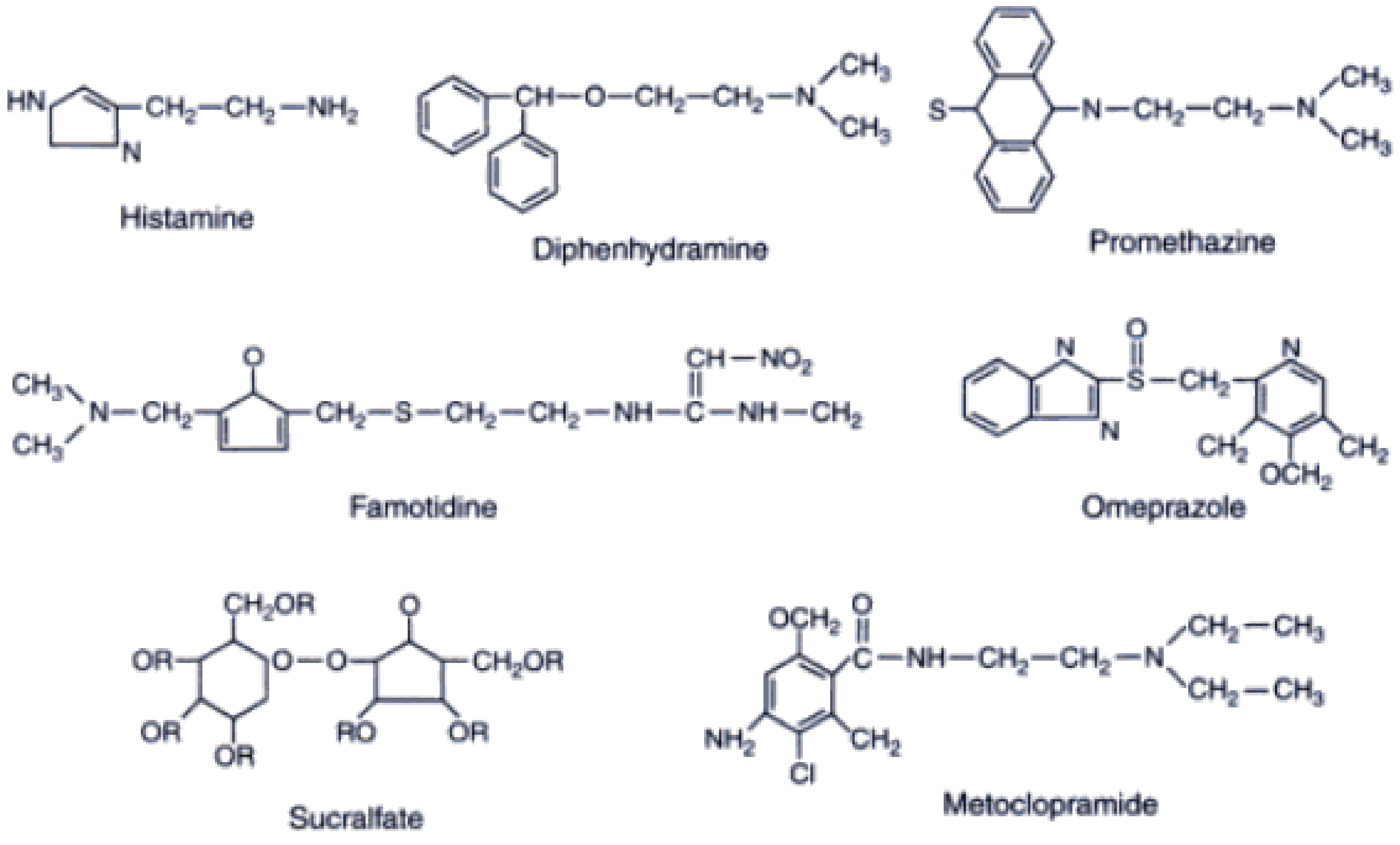

Figure 27–3. Chemical structures of selected gastrointestinal drugs.

used chronically. Although both gastric acid and pepsin are required for hydrolysis of proteins and other foods, achlorhydria is rarely accompanied by malabsorption unless bacterial overgrowth occurs. Achlorhydria can lead to malabsorption of certain nutrients, among them vitamin B_{12} and iron, as well as decreased absorption of some (weakly acidic) drugs.

H_2-Receptor Antagonists

H_2-receptor antagonists are reversible, competitive antagonists that reduce both the amount and the hydrogen ion content of gastric secretion and the amount of pepsin (Krishna and Ulrich, 1988) induced by a variety of secretogogues (Hirschowitz and Gibson, 1987). Secretion of intrinsic factor also is reduced, although this effect does not appear to be clinically relevant (Brunton, 1995a,b). Each antagonist is a congener of histamine, containing a bulky side chain (Brunton, 1995) (see Fig. 27–3). Cimetidine, ranitidine, and, to a lesser degree, famotidine, have been used to control gastric acid secretion in animals. Nizatidine is one of the newest of the H_2-receptor antagonists used by human patients. Each drug varies in potency, duration of action, disposition, and drug interactions (Bemis et al., 1989). Ranitidine is 5 to 12 times more potent as an inhibitor of gastric acid secretion than cimetidine, whereas famotidine is nine times more potent than ranitidine and 32 times more potent than cimetidine. Famotidine (see Fig. 27–3) has the longest duration of action (Howard et al., 1985). In animal models, including dogs, nizatidine is more potent than cimetidine (Price and Brogden, 1988). Although the H_2-receptor antagonists have prokinetic actions, they appear to have inconsistent effects on the rate of gastric emptying or lower esophageal sphincter pressure (Brunton, 1995a).

Disposition Cimetidine, the oldest of the clinically used H_2-receptor antagonist, is rapidly absorbed from the gastrointestinal tract, although food will delay the process. The drug undergoes hepatic metabolism and is about 70% bioavailable after oral administration. It is excreted in the urine in both the unchanged and conjugated forms. The plasma half-life is about 1 hour but may be prolonged in the presence of liver or kidney disease.

Ranitidine is less bioavailable (50%) than cimetidine after oral administration. Its elimination half-life is approximately 2½ hours. Absorption is not impaired by food as with cimetidine. It is minimally protein bound (15%). Hepatic elimination is responsible for 30% of an intravenous dose and 73% of an oral dose (Brogden et al., 1982).

Famotidine is only 37% bioavailable after oral administration due to poor oral absorption. In contrast, nizatidine is rapidly and completely absorbed (Krishna and Ulrich, 1988). Both drugs are largely eliminated unchanged in urine (Krishna and Ulrich, 1988). Nizatidine is almost exclusively eliminated by renal excretion, which suggests that it might be the preferred H_2 receptor antagonist for patients with hepatic disease. Its efficacy apparently has not been studied clinically in animals, although its safety has been established in healthy dogs (Bemis et al., 1989).

Drug Interactions Cimetidine can be involved in a number of drug interactions (Ames and Patterson, 1984; Brunton, 1995a). It, like all antisecretory drugs, impairs the oral absorption of a number of drugs (generally weak acids) due to alteration of gastrointestinal pH. Cimetidine also directly impairs the absorption of many drugs by binding to the drugs. Cimetidine is a potent microsomal enzyme inhibitor and will decrease the hepatic metabolism of concurrently administered drugs (Sedman, 1984; Gibaldi, 1992). Occasionally, this effect may be clinically useful as in the prevention of acetaminophen intoxication in cases of accidental overdose (Jackson, 1982). Impaired metabolism of other drugs can also, however, lead to clinically relevant toxicity of other drugs metabolized by the liver. Cimetidine also reduces hepatic blood flow by about 20% and has been shown to reduce the clearance of flow-limited drugs such as propranolol and lidocaine (Jackson, 1981). Unlike cimetidine, ranitidine and famotadine have limited to no effects on hepatic blood flow or on the metabolism of other drugs (or endogenous compounds). Drug interactions involving famotidine and nizatidine are rare.

Adverse Reactions The side effects seen with any of the H_2-receptor antagonists are generally minor even at relatively high doses. Thrombocytopenia has been reported. Although there have been a number of reported side effects for ranitidine in the human, limited experience to date in animals has not indicated any serious toxic manifestations from ranitidine. Famotidine and nizatidine are devoid of many of the side effects of cimetidine (Price and Brogden, 1988).

A clinically important disadvantage of H_2-receptor antagonists described in humans is relapse of gastroduodenal ulceration after H_2-receptor antagonist therapy is discontinued. Although several explanations for relapse have been offered, rebound hypersecretion of gastric acid appears to be most plausible (Guharoy, 1991; el-Omar et al., 1996; Fullarton et al., 1991). Suppression of gastric acid by H_2-receptor antagonists results in increased plasma gastrin concentrations as early as 3 hours after a single dose. Subsequent stimulation of gastric mucosal G cells results in gastric acid hypersecretion that becomes evident when the drugs are discontinued. The likelihood of hypersecretion is compounded by increased parietal cell receptor sensitivity, which apparently characterizes patients afflicted with ulcers (Marks et al., 1991). Among the H_2 receptors studied, cimetidine seems to be the most likely and famotidine or nizatidine the least likely to cause rebound gastric acid hypersecretion (Marks et al., 1991; Yamaji et al., 1991; Fullarton et al., 1991). Rebound hypersecretion can be minimized by tapering the dose as the drug is discontinued.

Clinical Use The principal therapeutic uses of H_2 receptor antagonists include uremic gastritis, gastric and duodenal ulcers, stress-related erosive gastritis, and hypersecretory conditions such as gastrinoma or systemic mastocytosis. Although H_2-receptor antagonists can be used to treat drug-induced (i.e., NSAID) ulceration, their efficacy is controversial and other more specific antidotes (i.e., PGE_1) should first or also be administered (Larsen et al., 1992). On the other hand, the drugs have proven beneficial in providing protection against gastric ulceration induced by a number of etiologic agents including aspirin and stress (Brunton, 1995a). Cimetidine and ranitidine also appear to be effective in controlling upper gastrointestinal bleeding when hemorrhage is not due to erosion of major blood vessels. Histamine (H_2) receptor antagonists have also been used in gastroesophageal reflux disorders, esophagitis, and duodenal gastric reflux. In exocrine pancreatic insufficiency, cimetidine or ranitidine, if given about 30 minutes before feeding, may decrease enzymatic and acid hydrolysis of replacement pancreatic enzymes added to food upon their contact with gastric secretions, thus improving the efficacy and decreasing the cost of their use. Patients suffering from short bowel syndrome may benefit from long term H_2-receptor therapy to decrease the hyperacidity associated with this syndrome. The H_2-receptor antagonists are sufficiently safe that high doses can be given in humans to maintain pharmacologic effects with once to twice daily dosing (Brunton, 1995a).

Proton Pump Inhibitors

Mechanism of Action Omeprazole (see Fig. 27–3) is the commercially available member of the newest gastric antisecretory drugs, the substituted benzimidazoles. These drugs are potent and irreversible antagonists of the H^+, K^+-ATPase proton pump, the final step in gastric acid secretion stimulated by any secretagogue. Omeprazole is approximately 30 times more potent as an antacid than is cimetidine (Lampkin et al., 1990). As a weak base, the drug is unstable in an acid environment and thus is formulated as encapsulated enteric coated granules (Lampkin et al., 1990). Drug dissolution occurs in the more alkaline environment of the small intestine. Because oral bioavailability increases with environmental intestinal pH, plasma drug concentrations tend to increase the first 4 to 5 days of therapy (Lampkin et al., 1990). Omeprazole selectively partitions from systemic circulation into the acidic environment of parietal cells (pK_a 1) compared with other cells (pK_a 5). In the acidic environment, the drug is protonated and subsequently further transformed to the active inhibitor. Potassium-adenosine triphosphate (H^+, K^+-ATPase), the energy source for the proton pump, is potently inhibited (Lampkin et al., 1990; Brunton, 1995a). The enzyme is permanently inhibited, and secretion of HCl will resume only after new molecules have been formed in the luminal membrane (Brunton, 1995a). Because the drug accumulates in parietal cells, there may be a lag time of 3 to 5 days before maximum effect is realized (Lampkin et al., 1990; Larsson et al., 1988). In addition, efficacy will be maintained at low plasma drug concentrations and for some time after the drug is discontinued. Because of these characteristics, omeprazole can be administered once a day (Larsson et al., 1988).

Secretory volume is not as affected as is acidity (Lampkin et al., 1990). In humans, omeprazole is highly (96%) bound to serum albumin and α_1-acid glycoprotein. Its apparent volume of distribution is 0.31 L/kg (Lampkin et al., 1990). Also in humans, drug elimination depends on hepatic metabolism to inactive metabolites, and elimination half-life is short (52 minutes) (Lampkin et al., 1990). Omeprazole has been studied in dogs and horses (Jenkins and DeNovo, 1990). In horses the elimination half-life of omeprazole is 30 minutes. Oral bioavailability is reduced, although therapeutic concentrations can be achieved.

Adverse Reactions Adverse reactions caused by omeprazole are limited because the drug is selective for the H^+,K^+-ATPase pump. An exception is the sequela of achlorhydria. Diarrhea and transient fluctuations in liver enzymes have been reported. Hypergastrinemia has been documented in human patients (Lampkin et al., 1990) after therapy with omeprazole, but rebound hypersecretion of gastric acid has apparently not been studied. Hypertrophy of gastric mucosa has been reported. A marked increase in gastric acid secretory capacity has been detected after omeprazole treatment, presumably owing to proliferation of an enterochromaffin-like cell mass (Waldon et al., 1996). Compared with cimetidine, omeprazole is less likely to be involved in drug interactions. Partial inhibition of drugs eliminated by selected cytochrome P450 enzymes has been reported for omeprazole (Andersson, 1991).

Clinical Use Omeprazole is the drug of choice for the treatment of the Zollinger-Ellison syndrome. In humans without gastrinomas, extended use of omeprazole is associated with complete antiacidity, which induces hypergastrinemia and gastric hypertrophy. Omeprazole has been used to control gastric acid secretion that has not responded to H_2-receptor antagonists, although its superiority to these and other antacid drugs has not been firmly established. Generally, however, studies support superiority of omeprazole compared with cimetidine for treatment of gastrointestinal ulceration, including response of pain (Lampkin et al., 1990).

Prostaglandin Analogues

In addition to receptor antagonism, gastric acid secretion can also be modulated by prostaglandins of the E series. Their actions appear to be mediated by interaction with a basolateral membrane receptor. Intracellular concentrations of cAMP decrease, which in turn decreases protein kinase activity and hydrogen ion concentration (Fig. 27–5) (Wolfe and Soll, 1988). Misoprostol is a methyl ester analogue of prostaglandin E_1. As such it is pharmacologically active after oral administration with effects lasting longer than endogenous prostaglandins (Misoprostol Monograph, 1990). Its action tends to be restricted to the local environment, with systematically absorbed drug rapidly metabolized by the liver (Jones and Bailey, 1989). Misoprostol does not appear to alter serum gastrin levels, and rebound acid hypersecretion has not been reported (Jenkins and DeNovo, 1990). Basal, nocturnal, and food-induced gastric acid secretion is inhibited by misoprostol. The drug may not, however, be as effective as selected H_2-receptor antagonists in decreasing intraluminal pH and appears less effective in controlling pain associated with hydrochloric acid secretion. Unabsorbed drug that reaches the intestine can cause intestinal secretion, smooth muscle contraction, and thus diarrhea, but these side effects may be resolved after several days (Misoprostol Monograph, 1990).

Figure 27–5. Protective mechanisms mediated by prostaglandin E against gastroduodenal ulceration provide targets for drug therapy. Bicarbonate secretion acts to neutralize gastric acid; mucus protects against hydrochloric and bile acids. The rapid turnover of epithelial cells is paramount for rapid healing if damage occurs. Mucosal blood flow not only provides critical oxygen and nutrients necessary for epithelialization but also removes H$^+$ ions that have penetrated the protective barrier. Other protective factors include mechanisms to control gastric hydrochloric acid secretion and the production of protective factors that scavenge mediators capable of cell damage.

Cytoprotective Drugs

Antacids

Antacids chemically neutralize HCl present in the gastric lumen such that luminal pH is increased to an acceptable level (Morrissey and Barreras, 1974). Reaction with HCl results in the generation of chlorides, water, and carbon dioxide (Brunton, 1995a). Inactivation of pepsin and binding of bile salts by some products (e.g., aluminum hydroxide) are also important. Finally, some products (e.g., aluminum hydroxide) also induce the local synthesis of mucosal protectants (e.g., prostaglandins and sulfhydryls) (Vergin and Kori-Lindner, 1990; Szelenyi and Brune, 1986). Effective antacids should raise the pH of gastric fluids to at least 3 or 4 without causing systemic alkalosis. Among the antacids clinically used, calcium and sodium carbonate are considered fast-acting, magnesium hydroxide slow to moderate, and aluminum hydroxide slow-acting. However, release of CO_2 from carbonates can cause abdominal distention and belching (Brunton, 1995a). The action of gastric antacids is usually transient and lasts only 1 to 2 hours. The presence of food, however, which by itself increases gastric pH to about 5, prolongs the neutralizing effects of antacids for about 2 hours (Brunton, 1995a). Neutralization of acid in the stomach antrum removes negative feedback control of gastrin release, which in turn leads to elevated gastrin levels and enhanced HCl secretion, with increased tone of the lower esophageal sphincter. In the past, antacid administration was recommended at 4- to 6-hour intervals to minimize rebound hypersecretion. In human patients, however, administration with each meal has proved more convenient yet equally efficacious. Factors complicating rational antacid therapy are rate of acid secretion; duration of time the antacid remains in the stomach; the potency of the antacid; and adverse effects (Siepler et al., 1986).

The major nonsystemic antacids used in veterinary medicine are salts of aluminum, magnesium, and calcium used either alone or in combination with each other or with various protectants, adsorbents, and astringents. One gram of these compounds generally neutralizes 20 to 35 mEq of acid in vitro. Aluminum hydroxide is a good adsorbent (of bile acids and pepsin), as well as an antacid. It tends to provide prolonged antacid effects (Brunton, 1995a). In addition, it stimulates local prostaglandin production in the intestinal mucosa (Vergin and Kori-Lindner, 1990). Aluminum preparations tend to cause constipation and are often mixed with magnesium salts to prevent this side effect. Aluminum hydroxide decreases phosphate absorption by forming insoluble aluminum phosphates in the intestine and is used to control serum phosphorus in patients with renal disease. Note that prolonged administration with meals may cause hypophosphatemia in patients.

Magnesium-containing products can raise gastric pH higher than aluminum-containing antacids (9.0 vs. 4.0) (Morrissey and Barreras, 1974). Magnesium hydroxide is the most commonly used form of magnesium. Magnesium salts tend to be laxative and are often found in combination with aluminum and calcium salts. Their cathartic effects result from soluble but unabsorbed magnesium salts that remain in the intestine and retain water. The neutralizing effect of magnesium hydroxide is prompt and prolonged. Up to 20% of the magnesium is absorbed in normal circumstances, and in the presence of renal dysfunction repeated administration can result in hypermagnesia. Combination antacid products containing both aluminum and magnesium are often used to balance the adverse effects of each cation or bowel function (Siepler et al., 1986).

Calcium carbonate is a rapidly acting, potent antacid with a prolonged duration. Slowly developing metabolic alkalosis, gastric acid rebound, hypercalcemia, and calciuria with metastatic calcification and urolithiasis, hypophosphatemia, and constipation are, however, potential side effects that may occur after chronic administration of calcium carbonate (Siepler et al., 1986). In addition, interference with calcium-dependent processes may lead to excessive gastrin and HCl secretion (Brunton, 1995a).

Antacid therapy may alkalinize the urine. The rate of elimination of renally eliminated weak acids will be increased (e.g., nonsteroidal anti-inflammatories, phenobarbital) whereas that of weak bases is decreased (Brunton,

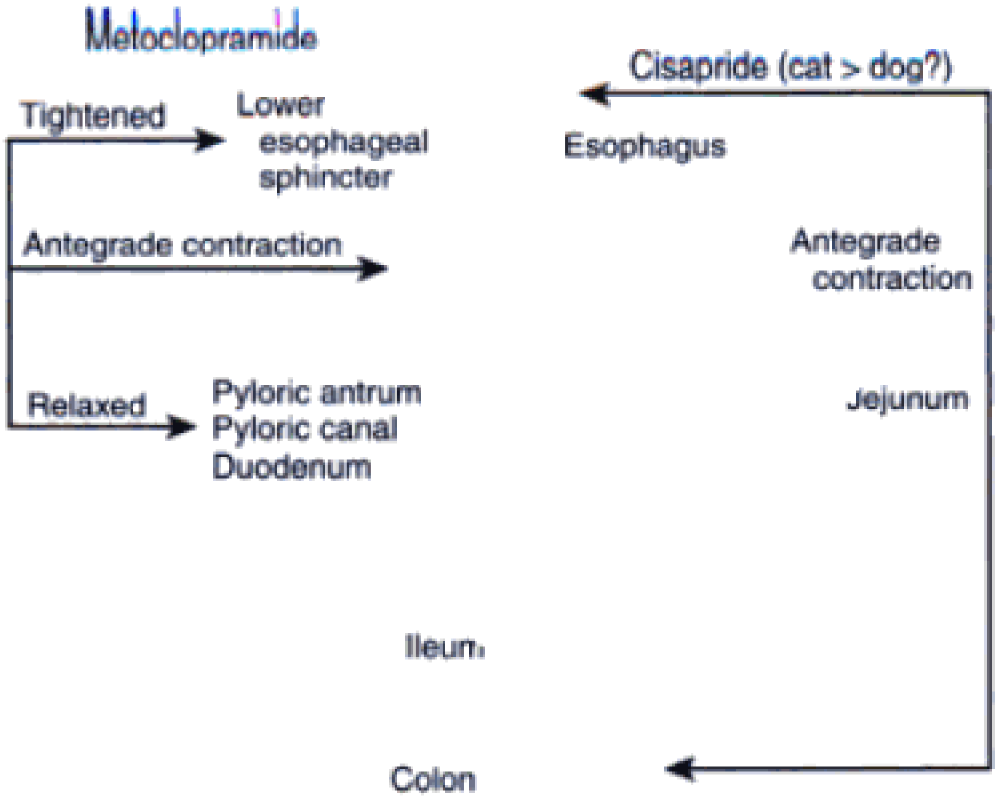

Figure 27–8. The sites of action of two clinically useful prokinetic drugs. In vivo, at standard doses, metoclopramide's actions are limited to the lower esophagus (feline more than canine), stomach, and upper duodenum, where it physiologically antagonizes vomiting. Cisapride appears to increase motility throughout the gastrointestinal tract.

The peripheral effects, however, appear to be mediated by effects on other local neurotransmitters, particularly dopamine. Serotonin receptors also may play a role (Reynolds, 1989). Dopamine via D_2 receptors has an inhibitory effect on smooth muscle of the stomach, duodenum, and colon and has been implicated as a mediator of receptive relaxation in dogs (see Fig. 27–7) (Reynolds, 1989). Dopamine may exert its inhibitor effect through inhibition of acetylcholine, thus explaining the complex mechanism of metoclopramide (Reynolds, 1989). Peripheral antidopaminergic effects of metoclopramide appear to reflect interaction with D_2 receptors (Reynolds, 1989). Metoclopramide physiologically antagonizes emesis by increasing the tone in the lower esophageal sphincter, increasing the force and frequency of gastric antral contractions (gastrokinetic effect), relaxing the pyloric sphincter, and promoting peristalsis in the duodenum and jejunum, resulting in accelerated gastric emptying and upper intestinal transit (Burrows, 1983).

Metoclopramide is well absorbed orally but undergoes significant first-pass metabolism with a bioavailability in the 50% to 70% range. Tissue distribution is rapid, and excretion is both renal and hepatic. The plasma half-life in the dog is only 90 minutes, and, as such, metoclopramide has a short duration of action (Burrows, 1983). Dose-dependent CNS side effects include nervousness, restlessness, listlessness, depression, and disorientation (Reynolds, 1989; Clark and Becht, 1987; Burrows, 1983). Extrapyramidal antidopaminergic effects include tremors and motor restlessness. Gynecomastia due to enhanced release of prolactin has been reported in humans (Reynolds, 1989). Gastrointestinal disorders may also be observed, with constipation being common with long-term use.

As an antiemetic, the main indications for metoclopramide include severe and intractable emesis caused by chemotherapy or other blood-borne toxins as well as nausea and vomiting associated with delayed gastric emptying, gastroesophageal reflux, reflux gastritis, and peptic ulceration. As a prokinetic, metoclopramide is indicated for treatment of a variety of gastric motility disorders, including gastric dilation, volvulus, postoperative ileus, gastric ulceration, and idiopathic gastroparesis (Albibi and McCallum, 1983). Metoclopramide is contraindicated in gastrointestinal obstruction or perforation, potentially in epilepsy, and for patients receiving neuroleptics. Because of their anticholinergic effects, atropine and the opioid analgesics antagonize the action of metoclopramide.

Domperidone

Domperidone is a dopamine antagonist whose prokinetic properties are similar to those of metoclopramide (Takahashi et al., 1991). It has no cholinergic activity and is not inhibited by atropine. Domperidone does not cross the blood-brain barrier as readily as metoclopramide. Like metoclopramide, however, domperidone can affect central dopamine receptors and thus modulate temperature control, prolactin secretion, and activity at the CRTZ (Reynolds, 1989). Extrapyramidal side effects are rare. Domperidone acts peripherally to coordinate antroduodenal contractions. Its peripheral effects accelerate small intestinal transit, but colonic activity is apparently unaffected (Clark and Becht, 1987).

Cisapride

Cisapride has the broadest spectrum of action of the prokinetic agents (McCallum et al., 1988). It causes dose-dependent increased activity at all sites (stomach, jejunum, ileum, and small and large colon) (see Fig. 27–8). Because it does not interact with dopamine receptors, its use is not associated with extrapyramidal side effects (Demol et al., 1989). Its prokinetic actions appear to reflect indirect stimulation of cholinergic nerves; serotonin appears to mediate this effect through 5-HT_4 receptors (see Fig. 27–7). Because secretion is not enhanced, stimulation probably occurs at the level of the myenteric plexus (Reynolds, 1989). Like metoclopramide and domperidone, antroduodenal contractility is enhanced by cisapride (Reynolds, 1989). Prokinetic effects have been documented in the esophagus, stomach, small bowel, and colon (Reynolds, 1989). Because 75% of the canine esophagus is skeletal muscle, however, the prokinetic effects are likely to be less in dogs.

Well absorbed after oral administration, cisapride undergoes first-pass metabolism, with oral bioavailability in humans being 50%. Metabolites are apparently inactive. Volume of distribution is large (2.4 L/kg) in humans, and elimination half-life is 10 hours. Cisapride kinetics have been reported in the cat (LeGrange et al., 1997). Oral administration is characterized by 30% bioavailability, and the elimination half-life approximates 5 hours. A dose of 1 mg/kg every 8 hours or 1.5 mg/kg every 12 hours is recommended based on these data. Elimination may be prolonged in the presence of liver disease (McCallum et al., 1988). Indications for use of cisapride are similar to those for metoclopramide (excluding dopaminergic effects). Indications in humans include any disorder associated with impaired gastric emptying as well as gastroesophageal reflux. Comparison between cisapride and ranitidine, an H_2-receptor antagonist, for the treatment of gastroesophageal reflux reveals both to be effective (Pouderoux and Kahrilas, 1995).

Cisapride causes prolongation of the QT interval and torsades de pointes, leading to sudden cardiac death. The risk is greater when cisapride is combined with other drugs that inhibit the cytochrome P450 enzyme responsible for cisapride metabolism in humans (e.g., clarithromycin, itraconazole) (Piquett, 1997).

DRUGS AFFECTING THE INTESTINAL TRACT

Physiology, Pathophysiology, and Motility

Drug therapy for diarrhea tends to be nonspecific. Therapy might, however, target the type of diarrhea. Diarrheas can be classified as inflammatory or infectious, osmotic (including malabsorption), and secretory. The goal of antidiarrheal therapy generally is to reduce the discomfort and inconvenience of frequent bowel movements, and, when indicated, replaced fluids or electrolytes lost with diarrhea.

Ordered intestinal motility results from a balance between hormonal, myogenic, and neurogenic factors. It is a complex, physiologic event (Crema and De Ponti, 1989). Several forms of coordinated movement occur in the intestine that serve to mix the liquefied contents and propel it in an aboral direction. Rhythmic segmentations are caused by simple nonprogressive contractions of circular muscle. They result in mixing movements and promote absorption of intestinal lumen contents by narrowing the effective diameter of the intestinal lumen, thus impeding flow of fluid intestinal contents. Contraction of longitudinal smooth muscle results in peristaltic movements and aboral movement of intestinal contents. Although peristaltic activity is mainly propulsive, it also ensures mixing and successful absorption. Both longitudinal and circular smooth muscles are involved in peristaltic movements. Activity in the small bowel varies from that in the large bowel. Generally, slow waves occur continuously and propagate aborally. In the colon, slow waves are sometimes absent, and propagation may be variable (Crema and De Ponti, 1989). Intestinal motility is integrated at several levels: locally, at autonomic ganglia; and in the CNS at both spinal and supraspinal levels (Crema and De Ponti, 1989). Several types of muscarinic receptors have been identified pharmacologically (M1, M2, M3, and M4) in the gastrointestinal tract. M1 or M3 receptors interact with G protein and mobilize intracellular calcium; M2 and M4 receptors inhibit adenylcyclase and regulate ion channels. M1 receptors present in the myenteric plexus may inhibit motility via GABAminergic mechanisms. M2 receptors located presynaptically and postsynaptically mediate presynaptic inhibition of acetylcholine release. M3 receptors appear to be located on smooth muscle cells (Crema and De Ponti, 1989).

Absorption in the small intestine occurs first by passive sodium absorption across the luminal membrane and second by active secretion of the sodium across the basolateral membrane. Water osmotically follows sodium into the lateral intracellular space. The electrochemical gradient caused by sodium movement facilitates chloride diffusion into the cell (Hughes, 1983). A specific brush border carrier for NaCl cotransport accomplishes absorption. Nutrients such as glucose and other organic solutes, however, facilitate a solvent drag of water and electrolytes as they enter cells (Hughes, 1983).

Secretion in crypt cells of the intestinal epithelium is initiated by intracellular signaling (cAMP) or calcium. Increased chloride conductance into the lumen results in sodium recycling first through the lateral intercellular space and second into the lumen. Although NaCl cotransport is inhibited, NaCl movement due to solvent drag (i.e., that mediated by nutrients) is not (Hughes, 1983).

Increased amounts of fecal water reflect either diminished absorption or a net secretion (accumulation) of fluid into the lumen of the intestine. In all diarrheal states, increased fecal water loss is associated with an overall secretion of electrolytes and water in selected segments of the gastrointestinal tract. The absorptive capacity of the alimentary canal is overwhelmed distal to the site of secretion. Sodium-absorbing cells are present predominantly on the villi, and chloride-secreting cells are located primarily in the crypts. Increased intestinal cell cyclic 3′5′ adenosine monophosphate, cyclic guanosine 3′5′ monophosphate, and Ca^{2+} (through calmodulin) all have similar effects on sodium-absorptive and chloride-secretory cells, producing diminished sodium absorption and increased chloride secretion with a net efflux of water into the lumen. Cholera enterotoxin is the best known intestinal secretagogue (Hughes, 1983), but several hormones, including vasoactive intestinal peptide (VIP), GIP, CCK, secretin, glucagon, and PGE_1, are also associated with net fluid accumulation as are other infectious agents (e.g., *Escherichia coli*, *Staphylococcus* sp.) (Hughes, 1983). Several laxative agents such as bile acids and ricinoleic acid are also thought to act through this mechanism. The exact role of intestinal motility in the alteration of fluid and electrolyte movement is still unclear. The role of mucosal permeability or mucosal damage in the genesis of fluid accumulation within the gut lumen is still obscure.

Modulators of Intestinal Motility and Secretions

Substantial evidence exists linking gastrointestinal secretion with gastrointestinal motility (Greenwood and Davison, 1987). Increased motility is usually accompanied by increased fluid and electrolyte secretion (Greenwood and Davison, 1987). Rehydration followed by oral replacement therapy has received much attention as the preferred treatment for diarrheas associated with infectious agents (Hughes, 1983). Suitable solutions contain K^+, HCO_3^-, Na^+, and glucose in sufficient quantities to replace stool losses (Hughes, 1983).

Anticholinergic Agents

Parasympatholytic or antimuscarinic agents diminish motor and secretory activity of the gastrointestinal tract. Tone and propulsive movements are decreased (Fig. 27–9), and these agents will often relax spasm of visceral smooth muscle. Such antimuscarinic drugs are thus known as *antispasmod-*

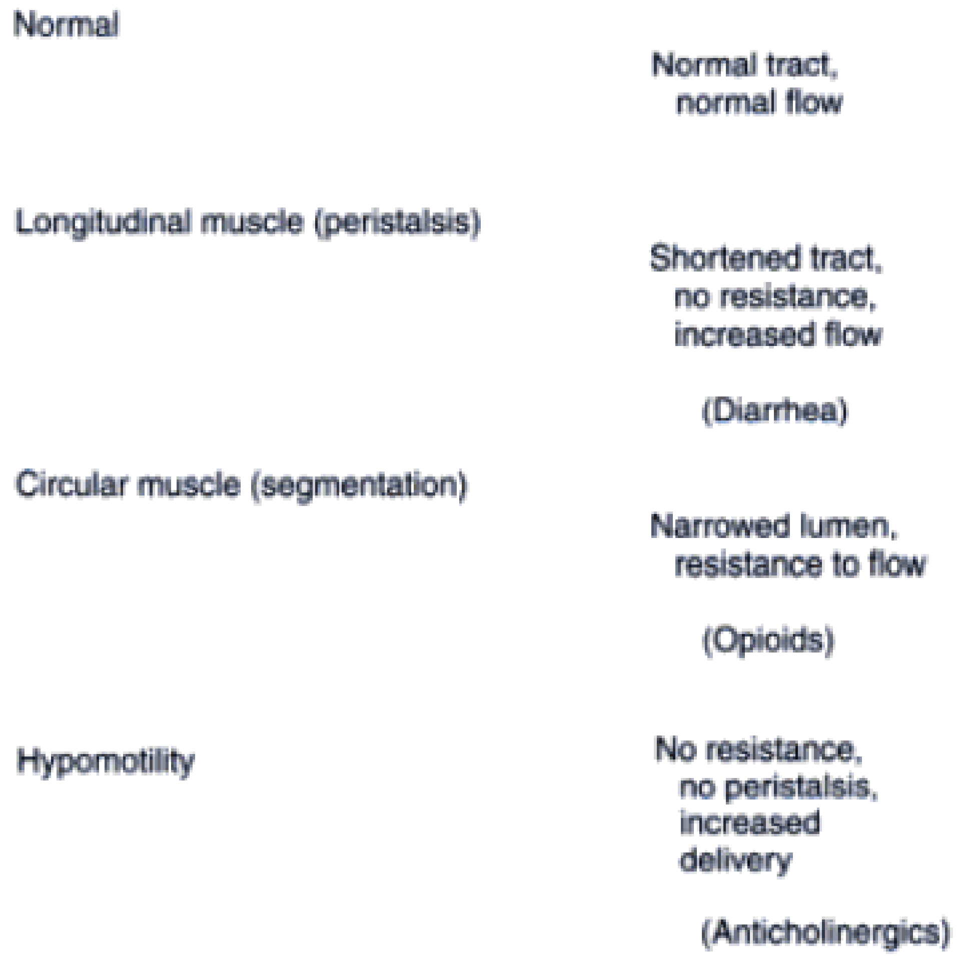
Normal
Normal tract, normal flow
Longitudinal muscle (peristalsis)
Shortened tract, no resistance, increased flow
(Diarrhea)
Circular muscle (segmentation)
Narrowed lumen, resistance to flow
(Opioids)
Hypomotility
No resistance, no peristalsis, increased delivery
(Anticholinergics)

Figure 27–9. The sequelae of smooth muscle contraction in the intestines vary with the type of muscle. Longitudinal muscle contraction shortens the gastrointestinal tract; peristalsis thus forces expulsion of luminal contents. Contraction of circulatory muscle causes segmentation or resistance to outflow. This effect predominates with opioids. Anticholinergic drugs impair both types of muscle activity.

ics or *spasmolytics*. Although cholinolytic agents are commonly used as spasmolytics in antidiarrheal mixtures, severe forms of diarrhea may occur in the presence of intestinal paralysis or ileus induced by the cholinergics. The main benefit of anticholinergic agents may be related to their ability to reduce intestinal secretions.

Antimuscarinic agents used as spasmolytics include the belladonna alkaloids (atropine and hyoscine), their congeners (atropine methonitrate, homatropine methobromide, hyoscine butylbromide, anisotropine methylbromide), and synthetic cholinolytics (aminopentamide, dicyclomine, glycopyrrolate, mepenzolate, oxyphenonium, propantheline, benzetimide, pipenzolate, clidinium, camylofine). Many of the belladonna alkaloid derivatives are substituted tertiary amines and thus may have undesirable CNS and other systemic effects. The synthetic groups are mostly substituted quaternary amines and are devoid of CNS effects. Xerostomia, loss of lens accomodation, urinary retention, constipation, tachycardia, and CNS stimulation are potential side effects that may be encountered when parasympatholytics are administered.

Opioids

Endogenous Opiates

Opiates have been used since antiquity to control diarrhea, and they remain the cornerstone of nonspecific antidiarrheal therapy for humans (Brunton, 1995b). Opioids appear to influence normal gastrointestinal physiology (Kromer, 1988). Opioids may stimulate gastrointestinal motility both locally and by central effects in the brain or spinal cord (Demol et al., 1989). Both opioid peptides and opioid receptors have been identified throughout the gastrointestinal tract. The number and type of receptor varies with the species. In humans, activation of both appears to enhance electrolyte absorption (Brunton, 1995b). Endogenous opioids are present in high concentrations in the intestinal wall. Biosynthesis of enkephalins have been demonstrated in the myenteric plexus of some species. In addition, antral G cells are thought to be capable of synthesis of enkephalins or endorphins. β-endorphin and dynorphine have also been demonstrated. In cats, enkephalin has been detected in both myenteric and submucosal plexi. In contrast to other species, the predominant location of enkephalin neurons in dogs is the submucosal plexus. Opioid nerve fibers have also been documented in the lower esophagus, pyloric junction, and cardiac and ileocecal regions. Specific degradative enzymes for the opioid peptides have also been identified in similar locations (Kromer, 1988).

Location of opioid receptors in the gastrointestinal tract has been based on the physiologic effects of opioid agonists and antagonists (Kromer, 1988; Allescher et al., 1989; Shook et al., 1989). Both in vitro and in vivo preparations have been studied, often with conflicting results. High-affinity, reversible, and saturable binding of opioid receptors has been identified in longitudinal and circular smooth muscles and the myenteric and submucosal plexi. Binding has also been noted in the muscularis mucosae. Although multiple opioid receptors have been identified, μ-type and δ-type opioid binding sites appear to predominate among the species. Morphine acts to stimulate μ-receptors of the myenteric plexus, thus inducing migrating motor activity inthe duodenum and jejunum. The relative importance of different receptor types in the control of intestinal peristalsis has not been established.

Gastrointestinal Motility

In vitro studies indicate that normal functions attributed to endogenous opioids in the gastrointestinal tract include modulation of gastrointestinal motility and gastrin release. In vitro peristalsis results from phasic circular muscle contractions that travel down the intestinal segment, thereby expelling contents distally. It is easily distinguished from in vitro pendular movements or segmentations. Exogenous opioids depress the normal peristaltic reflex and thus appear to control normal peristalsis (see Fig. 27–8). This effect has been repetitively demonstrated with the use of the pure antagonist naloxone, which consistently increases peristaltic activity.

The intestinal opioid mechanism has been documented throughout the intestinal tract by in vitro studies, although its functional role appears to increase from duodenum to ileum. Endogenous opioids may thus be partially responsible for the *gradient of intestine*, a term that describes the oral to aboral phenomenon of decreasing frequency of peristaltic waves and decreasing sensitivity to distension stimuli (Kromer, 1988). Gastrointestinal opioids are thought to be subject to feedback control (Kromer, 1988). The effect of opioids on gastrointestinal sphincters varies. The net effect may be dose dependent. For example, excitation (contraction) of the choledochoduodenal junction in dogs occurs with some drugs at doses lower than those causing inhibition. Although species differences have been documented for the sites of action, receptor populations, and motility caused by opioids, these differences are more often quantitative than qualitative (Kromer, 1988).

The widely accepted mechanism of opioid actions in the gastrointestinal tract is inhibition of ACh release. Modulation of the effects of acetylcholine already released is thought, however, to be important for the effects of opioids on peristalsis. Intracellular mechanisms may involve increased calcium-dependent potassium conductance and hyperpolarization. The spasmogenic effect caused by opioids is antagonized by atropine. Opioids also reduce calcium entry during the action potential and deplete neurons of calcium. Although acetylcholine is generally recognized to be the predominate neurotransmitter modulated by the opioids, modulation of other endogenous mediators such as serotonin are also likely to be involved (Kromer, 1988).

Gastrointestinal Secretion

As with motility, the effect of opioids on gastric acid secretion varies with the study, species, and opioid. Opioids enhance gastric acid secretion mediated by histamine in in vitro studies, but the effect on acetylcholine-induced secretion varies in in vivo studies. Dose dependency may account for some of the variability, with excitation or enhancement of basal secretion occurring at lower doses and inhibition at higher doses. A dual effect on stimulated gastric acid secretion appears to be mediated both peripherally and centrally (Kromer, 1988).

In contrast to gastric secretion, the effect of opioids on intestinal secretion appears to be consistent among the species (Kromer, 1988). Opioids stimulate the net absorption of water and electrolytes in enterocytes of both small and large intestines in a variety of species. In vitro studies indicate that these peripheral effects are mediated by δ-receptors. Receptor types may, however, vary with the site. These effects, which may reflect facilitated absorption or inhibited secretion, are largely responsible for the antidiarrheal properties of the opioids. Several mediators, acting both centrally and peripherally, may signal the antisecretory effect of the opioids. The ability of opioids to modulate secretion is likely to vary with the chemical mediator. Presynaptic inhibition of ACh release and inhibition of prostaglandin-mediated adenylate cyclase activity have been implicated as the site of inhibition. Sodium, but not chloride, appears to be the ion negatively influenced. The opioids also act centrally to decrease secretions in the intestine, perhaps by altering the sympathetic nervous system. Antisecretory effects may involve norepinephrine and its effects on vasoinhibitory peptide, prostaglandin E, or ACh (Demol et al., 1989). Decreased intracellular free calcium also has been implicated as a possibility. In contrast to water and electrolyte secretion, opioids act to increase bicarbonate secretion from the gastric and duodenal mucosa (Kromer, 1988).

Drugs

Diphenoxylate hydrochloride is a meperidine derivative used specifically to control diarrhea. It is often administered in combination with atropine-like compounds. Its action is largely dependent on a direct peripheral effect on the gastrointestinal wall. Because diphenoxylate can penetrate the blood-brain barrier, systemic opiate effects may occur. The potential for drug abuse has led to its designation as a Schedule V drug. Atropine is added to diphenoxylate as a deterrent to substance abuse by its bitter taste and drying effect on salivary secretions.

Loperamide hydrochloride, a butyramide derivative, is an orally active and effective antidiarrheal agent used for symptomatic control of acute and chronic nonspecific diarrhea. Unlike diphenoxylate, systemic opiate agonist effects do not appear to occur after oral administration of loperamide, and there are few side effects. Although loperamide has some structural similarities to diphenoxylate, it does not cross the blood-brain barrier, and it differs both qualitatively and quantitatively from diphenoxylate and difenoxin in its pharmacologic actions (Schiller et al., 1984). Intestinal transit time and intestinal luminal capacity increase after treatment with loperamide (Demol et al., 1989).

Miscellaneous Antisecretory Drugs

There are a number of potentially useful drugs that have not been extensively studied but for which there is some evidence of clinical benefit. Glucocorticoids have been found to be beneficial in treating refractory chronic diarrheal disease as well as chronic inflammatory diseases of the intestinal tract. Glucocorticoids stimulate active sodium absorption in the jejunum, ileum, cecum, and colon. Because of many undesirable side effects when used chronically, the glucocorticoids should not be used on a routine basis to treat diarrhea.

Adrenergic agents appear to act predominantly by increasing basal fluid absorption and do so at very low concentrations. The mechanisms involved are unclear. Clonidine and other α_2-adrenergic agonists are potentially useful in this regard. Calcium/calmodulin antagonists may act by stimulating active absorption as well as by inhibiting intestinal secretion, but the precise mode of action of these drugs is not clear. Several drugs with this effect have been found to be useful in the control of certain forms of secretory diarrhea. Examples include chlorpromazine and trifluoperazine. Nonsteroidal anti-inflammatory drugs such as aspirin, indomethacin, flunixin, and the subsalicylate of bismuth subsalicylate inhibit the cyclooxygenase pathway of arachidonic acid metabolism and thereby suppress the formation of prostaglandin mediators. The roles of various prostaglandins in intestinal motility as well as in absorption and secretory processes is complex, and the inhibition of prostaglandin synthesis will not consistently influence secretory diarrheal states.

The NSAIDs may, however, prove to be therapeutically beneficial in some acute and chronic diarrheal syndromes. Asulfidine (sulfasalazine) is a product that is metabolized to 5-aminosalicylic acid and sulfadiazine by colonic microbes (Robinson, 1989). Either of the two components (i.e., anti-inflammatory vs. antimicrobial) may be efficacious in the treatment of chronic inflammatory bowel diseases such as ulcerative colitis. As with all aspirin-containing compounds, caution is indicated when a sulfasalazine is used in the cat because salicylic acid released in the colon can be subsequently absorbed. In an effort to reduce exposure to sulfonamides, mesalamine was developed as an alternative to asulfidine. Mesalaminie represents the active anti-inflammatory component (i.e., 5-amino salicylic acid). It is available in slow-release tablets (designed for human use) that are intended to act locally and as an enema preparation. The aspirin component of the drug may be 30% or more bioavailable and care should be taken to avoid aspirin toxicity, especially in cats. The enema contains sodium benzoate as a preservative, which also should be avoided in cats.

Cholestyramine resin is a resin that binds bile acids and endotoxin within the lumen of the intestine. It has been used in humans principally for control of hypercholesterolemic syndromes and for treatment of intractable diarrhea (see gastrointestinal protectants and adsorbents).

GASTROINTESTINAL PROTECTANTS AND ADSORBENTS

Compounds that are not absorbed from the gastrointestinal tract and either line the mucosal surface or adsorb toxic compounds are often incorporated into antidiarrheal mixtures. The protectants seemingly produce a coating of the gastrointestinal epithelium that prevents irritation or erosion by potentially harmful substances. The adsorbents physically bind chemical compounds, which precludes their absorption, and they are then eliminated in the feces. Use of these two therapeutic classes is obviously directed at potentially harmful agents of either inorganic or organic nature. Adsorbents will also, however, bind concurrently administered drugs used for therapeutic purposes.

Many protectants and adsorbents possess both properties to varying degrees. Those most frequently used are magnesium trisilicate, hydrated magnesium aluminum trisilicate (activated attapulgite), kaolin (natural hydrated aluminum silicate), aluminum hydroxide and phosphate, bismuth salts, calcium carbonate, pectin (natural polygalacturonic acids), and activated charcoal.

The combination kaolin/pectin product is dissolved in 20 parts water. Described as a demulcent and adsorbent, the drug supposedly binds and removes bacteria and their metabolic products and toxins. These effects are controversial. Although stool consistency may improve, studies do not indicate that fluid and electrolyte imbalance is corrected, nor is the course of disease shortened (Wilcke and Turner, 1987).

The insoluble bismuth salts have been used for over 400 years (DuPont, 1987). Products include bismuth subcarbonate, bismuth subnitrate, and bismuth subsalicylate. Bismuth subsalicylate is a crystalline 1:1 trivalent bismuth and salicylate compound. It is chemically transformed throughout the gastrointestinal tract to bismuth and salicylate. The drug has been shown to have both antisecretory and antimicrobial effects in several species (DuPont, 1987). The subsalicylate fraction has been shown to have antiprostaglandin synthetase effects, which would enhance its action in controlling diarrheal syndromes (Hughes, 1983). In people and cats, nearly all the salicylate is systemically available (Papich et al., 1987; DuPont, 1987). Caution is recommended in order to avoid salicylate toxicity in cats receiving this drug.

Activated charcoal has primarily adsorbent properties. Because of its broad spectrum of adsorptive activity and its rapidity of action, it is one of the most valuable agents for emergency treatment of certain cases of poisoning. It forms a stable complex with many substances and permits their evacuation from the body. Charcoal preparations vary according to the source of base material, surface area, capacity for drug binding and affinity, and avidity of drug binding (Watson, 1987). Source materials are usually lignite, wood, or peat. Activation forms more pores and enlarges the surface area. Activation time is directly correlated with the molecular size of the compounds adsorbed. Because most drugs are of an intermediate molecular weight, charcoals with pore sizes between 10 to 20 Å are most appropriate (Wilcke and Turner, 1987). Administration with a cathartic, such as sorbitol, is a common practice and facilitates rapid movement of the charcoal-toxin complex (Watson, 1987). Activated charcoal loses its efficacy as the time interval between treatment and toxin ingestion increases. The optimal dose and interval for administration of activated charcoal have not been well established (Watson, 1987), although a charcoal to toxicant ratio of 10:1 has been recommended (Wilcke and Turner, 1987). One source suggests treatment at 6-hour intervals (Watson, 1987). Powders are superior to tablets (Wilcke and Turner, 1987). Food generally decreases the efficacy of these products. In the common domestic species, 20 to 120 mg/kg powered activated charcoal is usually administered as a drench after mixing with water. An activated charcoal suspension may be used for gas lavage in simple-stomached animals.

Cholestyramine is a basic anion exchange resin that binds to acidic side chains such as those occurring in bile acids. To increase the number of basic binding sites, cholestyramine is attached to a polystyrene matrix that can act as a nonspecific adsorbent. As bile salts are bound in the gastrointestinal tract, lipoproteins, cholesterol, and neutral fat absorption is also decreased. Although specifically indicated for pruritis associated with increased bile acids, cholestyramine has also been used to symptomatically treat diarrhea. Nausea, constipation, steatorrhea, and decreased fat-soluble vitamin absorption are reported undesirable effects. The product should be administered in food or water (Wilcke and Turner, 1987).

LAXATIVES AND CATHARTICS

Laxatives and cathartics promote defecation by increasing frequency of defecation or fecal volume or consistency (Clark and Becht, 1987; Dimski, 1989; Horn, 1987; Burrows, 1984). Laxatives (or aperients) promote elimination of a soft-formed stool, whereas cathartics (or purgatives) tend to produce a more fluid evacuation. The difference between these two effects may be just a matter of dose, but in some instances laxatives are only capable of increasing the hydration or softness of the fecal mass without ever inducing catharsis. The enhanced intestinal transit times that occur with use of some of these cathartics are usually due to intrinsic local myenteric reflexes within the visceral smooth muscle or to stimulation of the cholinergic receptors of the extrinsic parasympathetic nervous system. Although a traditional classification of the group is presented here, it should be noted that many cathartics alter intestinal electrolyte transport to increase fecal water excretion, so the grouping of these compounds should perhaps more logically follow their effects on intestinal electrolyte movement.

A number of deleterious effects may occur with excessive or constant use of cathartics. Severe, continuous diarrhea and abdominal colic, leading to dehydration and even shock, may follow overdosage. Other potentially harmful effects include decreased sensitivity of the intestinal mucosa, megacolon, flatulence, loss of electrolytes (especially sodium, potassium, chloride, and bicarbonate), secondary aldosteronism, melanosis coli (anthraquinones), steatorrhea, protein-losing gastroenteropathy, excessive calcium loss with resultant osteomalacia, and exacerbation of inflammatory intestinal disease. Several drugs can also distribute into milk and adversely affect suckling young.

Emollient Laxatives

The emollient laxatives (lubricant laxatives, mechanical laxatives, fecal softeners) act unchanged. They are not absorbed to any appreciable extent and simply soften and lubricate the fecal mass, which in turn facilitates expulsion. Although not always reliable, particularly in the ruminant, they are used in all species.

Mineral oil (liquid paraffin) is very commonly employed as a lubricant laxative. Mineral oil is bland and generally safe to use, but a few untoward effects may be encountered. Chronic administration may impair absorption of fat-soluble vitamins, other nutrients, and coadministered therapeutic agents. Decreased irritability of the intestinal mucosa becomes evident with protracted use, and, paradoxically, chronic constipation may ensue. White or yellow soft paraffins are used most commonly for small animals as lubricant laxatives (e.g., feline hairballs). Several anionic surfactants are employed as fecal softeners. Examples include docusate sodium, previously called *dioctyl sodium sulfosuccinate* and *dioctyl calcium sulfosuccinate.*

Simple Bulk Laxatives

The simple bulk laxatives are hydrophilic in nature and are not digested within the gastrointestinal tract. They adsorb water and swell, and an emollient gel forms. The increased volume or bulk leads to distention, with resultant reflex contraction producing peristaltic activity. The feces remain soft and hydrated. Methylcellulose, carboxymethylcellulose sodium, and plantago seed (psyllium seed) are examples of simple bulk purgatives. Wheat bran, prunes, and other fruits also belong in this group. Besides the bulk action of these laxatives, it should be noted that the celluloses and hemicelluloses present are fermented in the hind gut by bacteria to produce volatile fatty acids and other products that in burn exert an osmotic effect and thus enhance laxative action. Meteorism and a very fluid stool often result from the use of simple bulk laxatives.

Osmotic Cathartics

The osmotic cathartics (saline purgatives) consist of salts or compounds that either are not absorbed at all or are only slowly and incompletely absorbed from the gastrointestinal tract. They retain or attract water into the intestinal lumen mainly by osmotic forces, although enhanced mucosal secretion of fluid may contribute to their effect. It is imperative that drinking water be freely available to an animal that has been dosed with an osmotic cathartic; use of this group of purgatives is contraindicated for dehydrated animals. In monogastric animals an effect may be generally anticipated in 3 to 12 hours. Magnesium salts are frequently used as saline purgatives. Magnesium ions also bring about release of cholecystokinin, which will increase peristaltic activity. Magnesium sulfate (Epsom salts), isotonic in a 6% solution, magnesium hydroxide, magnesium oxide (milk of magnesia), and magnesium citrate are the magnesium salts most commonly employed. The solutions need not be hypertonic to produce an effect. About 20% of the magnesium ions are absorbed when magnesium sulfate is dosed orally, and, if purgation does not occur, additional amounts of magnesium may be absorbed with subsequent depression of the excitable tissues in the body. This is even more likely to occur if renal function is impaired. Salts such as sodium sulfate (Glauber's salt), sodium phosphate, potassium sodium tartrate (Rochelle's salt), and even large quantities of sodium chloride are effective saline purgatives.

The sugar alcohols mannitol and sorbitol will also induce an osmotic catharsis as will the synthetic disaccharide lactulose, which is not digested in the small intestine because no specific enteric enzyme is present. It passes to the large intestine, where saccharolytic microflora ferment lactulose to produce acetic, lactic, and other organic acids, which in turn lower the pH of the colonic content and exert an osmotic effect. Water is attracted, the fecal mass softens, and colonic peristalsis ensues. Lactulose is used for chronic constipation and treatment of hepatic encephalopathy. Acidification of the contents of the large intestine favors a greater formation of the ionized and thus nonabsorbable ammonium ion rather than the readily absorbable ammonia molecule, which requires detoxification in the liver by the urea cycle. Hyperammonemia is thus decreased. Absorption of other toxic amines from the hind gut is also reduced by acidification of the contents. Some meteorism may be evident after administration of lactulose. Lactitol is an alternative osmotic cathartic. It is less sweet than lactulose and may be better tolerated.

Irritant Cathartics

Contact or irritant purgatives were thought to stimulate the mucosal lining of the gastrointestinal tract and thereby initiate local myenteric reflexes that would enhance intestinal transit. It now seems, however, that members of this group also provoke fluid accumulation in the lumen by activating secretory mechanisms. Irritant cathartics are regarded as being direct acting or indirect acting depending on whether a metabolic alteration is first required to form an active product. Some purgatives are so highly irritant that they may cause severe colic and superpurgation.

Several bland vegetable oils act as irritant purgatives. Their action is based on hydrolysis by pancreatic lipase in the small intestine and subsequent formation of sodium and potassium salts of the released fatty acids. These are then irritant soaps, which differ in potency depending on the oil used. Castor oil produces highly irritant ricinoleates; raw linseed oil leads to formation of less irritant linoleates; and olive oil leads to rather mild oliveates. The response to castor oil is prompt, and evacuation of the whole intestinal tract occurs, leading to an almost complete emptying. Moist bulky feeds are needed following purgation with castor oil. It is used mainly in nonruminants and often employed in calves and foals. The effect occurs in 4 to 8 hours in small animals.

Another group belonging in this class includes the diphenylmethane cathartics, which appear to have a greater effect on the large intestine. Their precise mechanism of action is unclear. An effect is usually seen within 6 to 8 hours, and excessive catharsis may occur with overdosage. Bisacodyl also is a diphenylmethane cathartic that inhibits glucose absorption and Na^+, K^+ ATP activity as well as altering motor activity of the visceral smooth muscle. Only about 5% of any dose of bisacodyl is absorbed. This agent is used both orally and by enema.

Enemas

Introduction of solutions or suppositories into the rectum to initiate the defecation reflex is a useful and simple method to correct or prevent constipation. Many preparations have successfully served as enemas, including soapy water (soft anionic soap), isotonic or hypertonic sodium chloride solutions, sorbitol, glycerol, surfactants such as sodium lauryl sulfoacetate, mineral oil, and olive oil. Enema preparations that contain phosphate should not be used in cats indiscriminately because they can precipitate potentially fatal hyperphosphatemia, hypocalcemia, and hypernatremia in cats (Atkins et al., 1985) or debilitated animals.

DRUGS AFFECTING THE LIVER

Cholagogues and Choleretics

Substances that cause contraction of the gallbladder are called *cholagogues*. The resistance of the sphincter of Oddi decreases as bile flows freely into the duodenum. Dietary fat and concentrated magnesium sulfate introduced directly into the duodenum through a tube exert a cholagogue effect through release of cholecystokinin/pancreozymin from the upper small intestine. Vagus stimulation also promotes contraction of the gallbladder.

Substances that increase secretion of bile by the hepatocytes are known as choleretics. A drug that stimulates the liver to increase output of bile of low specific gravity is called a *hydrocholeretic*. Production of bile is enhanced by stimulation of the vagus nerves and by the hormone secretin, which increases the water and bicarbonate content of bile. Physiologically, however, bile acid salts are mainly responsible for bile secretion—the so-called bile salt-dependent flow. A number of natural bile salts and several partially synthetic derivatives are used therapeutically as choleretics, including dehydrocholic acid, which is the most potent hydrocholeretic agent. Naturally occurring bile acid conjugates such as glycocholate and taurocholate enhance bile flow to a lesser extent. Bile salts used therapeutically have a dual action in directly promoting fat absorption and stimulating biliary secretion after they have been absorbed. Overdosage with these compounds tends to cause diarrhea.

Ursodeoxycholic acid (UDCA) is a natural bile acid constituting a very small portion of the bile acid pool. It is a degradation production of chenodeoxycholic acid. Among the bile acids, UDCA has the lowest hydrophobic-hydrophilic balance, the lowest capacity to make micelles, and the least potential for cholestatic or cellular membrane toxicity. Because cholestatic liver disease may be associated with accumulation of toxic bile acids, treatment with UDCA is appealing. Its efficacy in a variety of chronic liver diseases has been established. Its mechanism of action is not well understood but is probably related to bile acid metabolism (Heller et al., 1991). The use of UDCA in dogs suffering from selected cholestatic liver diseases has been documented (Meyer and Thompson, 1992). The disposition of UDCA has been studied in healthy cats (Nicholson et al., 1989). Sporadic vomiting and diarrhea were reported, but otherwise the drug appears to be safe. Scientific studies establishing its safety and efficacy in diseased animals are indicated.

Liver Protectants and Hepatotropic Agents

A comprehensive review of the treatment and management of hepatic disease is beyond the purview of this chapter. A selection of the drugs for treatment of liver failure are, however, listed and the rationale for their use noted. The major pharmacologic properties of many of these substances are discussed elsewhere in this volume. Hepatotropic agents are those having a special affinity for the liver or exerting a specific effect. Lipotropic agents hasten removal of fat or decrease its deposition in the liver. Use of lipotropic agents (choline, methionine, cysteine, betaine, lecithin, hydroxocobalamin) to increase mobilization of hepatic lipid is of proven value only in cases in which deficiencies of these substances exist. Deficiencies may be present in hepatic disease as a result of anorexia or insufficient dietary protein. Patients receiving and consuming a nutritious diet with adequate amounts of protein do not require supplementation with lipotropic agents, but their use has not been shown to be detrimental.

Choline

Choline is an indispensable metabolite of the body. It forms part of a number of endogenous compounds, particularly phospholipids. Phosphatidylcholine, lysophospholipids, plasmalogens, and sphingomyelins are phospholipids that contain choline. The mode of action of choline as a lipotropic agent is unknown. It may promote conversion of liver fat into choline-containing phospholipids, which are more rapidly transferred from the liver into blood. Choline is also essential for synthesis of phospholipids that are used in intracellular membranes concerned with lipoprotein synthesis. It is thought that the lipotropic agents methionine, betaine, and lecithin are effective because they contain choline or promote choline synthesis. The requirement for choline is well recognized in all conditions predisposing to fatty infiltration of the liver, including diabetes mellitus, malnutrition, and cirrhosis. Greater than normal quantities of choline seem to be needed for prevention of a fatty liver when the liver is already damaged. Choline deficiency is not the only cause of fatty liver in these conditions, nor will choline supplementation alone restore the liver to full functional competence. Choline is, however, extremely valuable in the multitherapeutic approach to prevention and cure of fatty liver.

Methionine

Methionine (L-methionine) readily donates its terminal methyl group for methylation of various compounds. Methionine is the principal methyl donor of the body and supplies its labile methyl group to ethanolamine to form choline. In addition to its methyl group, methionine (and cysteine) contains a sulfhydryl group, which appears to protect the liver against the noxious action of certain poisons. Orally administered methionine can, however, aggravate hepatic coma. Bacterial flora may convert methionine to mercaptan derivatives such as methanethiol and ethanethiol, which are themselves capable of inducing coma.

S-adenosyl-L-methionine (SAMe) is a naturally occurring endogenous methyl donor that in animal studies and clinical human studies improves biochemical parameters of liver function (Osman et al., 1993). Endogenous concentrations are reduced in cirrhotic liver disease patients. Production of sulfated compounds and phosphatidylcholine subsequently is reduced. In animal studies, SAMe improved bile secretion impaired by a variety of toxins and by pregnancy. Drug-induced hepatotoxicity and chronic liver disease were also reduced, without occurrence of serious side effects (Frezza et al., 1992; Manzillo, 1992). SAMe may act synergistically with urodeoxycholic acid for treatment of chronic progressive liver disease (Concari, 1996). Although absorbed well after oral administration, SAMe undergoes extensive first-pass metabolism (Osman et al., 1993). The compound is so hygroscopic that it is unstable unless protected; products in bubble packets might be the most prudent to use. Tablets cannot be broken without risk of loss of efficacy. Caution is recommended in purchase of SAMe; an independent investigation that compared the content of SAMe to the labeled amounts found 6 of 13 products to be mislabeled.

Lecithin

Lecithin contains choline as part of the molecule, which is liberated upon hydrolysis; it has been used in the dog as a lipotropic agent.

Selenium and Vitamin E

Selenium is now known to be essential for tissue respiration and is protective against dietary hepatic necrosis. It is extremely active and is only required in minute amounts. Vitamin E enhances the action of selenium, but both are required.

Selenium is an essential component of glutathione peroxidase, which catalyzes oxidation of reduced glutathione:

$$\text{(2)Glutathione-SH} + H_2O_2 \text{ (reduced form)} \rightarrow$$

$$\text{Glutathione-S-S glutathione} + 2H_2O \text{ (oxidized form)}$$

This glutathione peroxidase catalyzes removal of hydrogen peroxide and fatty acid hydroperoxides and thus exerts a protective effect on all cells, but especially on muscle, liver, and erythrocytes. The essential substances required for removal of peroxides are reduced glutathione and glutathione peroxidase. Vitamin E maintains glutathione in the reduced form by preventing formation of hydroperoxides; it is an antioxidant and thus reduces the amount of glutathione peroxidase required. Cysteine (*N*-acetylcysteine) is required for the reduced sulfhydryl radical of glutathione and is generally present in adequate quantities. Selenium and vitamin E enhance each other's action and together protect cells, especially hepatocytes, against harmful build-up of peroxides.

Vitamins

In the presence of liver disease, the fat-soluble vitamin K should be supplemented because hepatic stores may be quite rapidly depleted. The water-soluble vitamins of the B-complex group are frequently employed in therapeutic regimens for hepatic insufficiency. Few controlled studies have been carried out in this regard, but the rationale behind their clinical use is based on ensuring an adequate supply of metabolic cofactors.

Hydroxocobalamin

Hydroxocobalamin (previously called *vitamin* B_{12}) is stored in the liver, mainly in mitochondria, but there is also a microsomal fraction. This microsomal vitamin may be of importance in hepatic protein metabolism. Microsomal cell fractions from the livers of hydroxocobalamin-deficient animals are defective in the incorporation of methionine and alanine into protein. General liver protein synthesis is depressed in hydroxocobalamin deficiency.

Hydroxocobalamin has a lipotropic effect. It is involved in metabolism of labile methyl groups and in formation of choline. Hydroxocobalamin is also necessary for overall utilization of fat. When intake is low, however, the demand for this vitamin in hemopoiesis exceeds that for any other clinically recognizable physiologic function.

Glucose and Fructose

The liver resists many forms of injury when its stores of carbohydrate and protein are adequate; its efficiency is impaired when hepatocytes are laden with fat. Administration of a hypertonic solution of glucose and fructose produces favorable responses in a variety of hepatic abnormalities. A high glycogen content appears to protect liver cells from damage, and inhibition of gluconeogenesis (which occurs with administration of both insulin and glucose) may play an important role. Under the influence of insulin, hepatocytes undergo glycogen storage, hypertrophy, and hyperplasia. Insulin has a major anabolic effect on the liver.

AGENTS PROMOTING DIGESTIVE FUNCTIONS

Several preparations are used therapeutically to control specific gastrointestinal diseases by promoting digestive processes. These digestants generally consist of normal digestive enzymes or related substances that are used for replacement therapy in deficiency states.

Digestive Enzymes

Pepsin preparations are administered with hydrochloric acid to treat gastric achylia. Pancreatic extracts that stimulate pancreatic exocrine secretions are of therapeutic benefit in cases of chronic pancreatitis and pancreatic hypoplasia, in which glandular function is diminished or destroyed. Pancreatin (Panteric, Stamyl, Viokase) obtained from hog pancreas is the major ingredient of most commercial pancreatic enzyme preparations. Enteric-coated preparations to prevent destruction of pepsin in the stomach are generally thought to be better than noncoated preparations. In a few instances, enteric-coated preparations are the most effective in dogs with pancreatic insufficiency; they are added to food and must be provided with each meal. Dosage is adjusted to obtain a normal stool. Simultaneous administration of nonsystemic alkalinizing agents to maintain an optimal pH range for enzyme activity has not proved successful clinically. However, the administration of cimetidine about half an hour before dosing with pancreatic extract does limit gastric inactivation of the enzymes. Proper dietary control is also essential for the successful management of animals suffering from pancreatic insufficiency.

Bile acids and their salts promote absorption of long-chain fatty acids and fat-soluble vitamins. They also act as choleretics (discussed previously). Examples include dehydrocholic acid (Decholin) and chenodiol (previously named chenodeoxycholic acid).

Diastases are amylolytic enzymes obtained from malt and *Aspergillus oryzae* and are used for replacement of pancreatic α-amylase and to control flatulence caused by gas produced from soluble carbohydrates by bacterial flora.

TREATMENT OF SPECIFIC DISORDERS OF THE GASTROINTESTINAL TRACT

Diseases of the Oral Cavity

The primary treatment for the *feline eosinophilic granuloma complex* is glucocorticoids (Smith, 2000), given orally (prednisone, 1 to 2 mg/kg bid), subcutaneously (methylprednisolone acetate, 20 mg every 2 weeks), or intralesionally (triamcinolone, 3 mg each week). Progestational compounds such as methylprogesterone may prove beneficial, but side effects associated with long-term use (including hyperadrenocorticism and diabetes mellitus) should limit their use to cases that have not responded to any other (properly administered) drug therapy. Up to 50% of treated cats may relapse. *Stomatitis* may be a reflection of an autoimmune skin diseases, renal disease, microbiologic infection (viral, bacterial, or fungal) or may be idiopathic in nature. Antimicrobial therapy should be considered in cases of idiopathic stomatitis; therapy may be necessary on a chronic, intermittent basis. Drugs should target anaerobic organisms (e.g., metronidazole, a penicillin derivative, or clindamycin). Treatment of bacterial stomatitis is discussed further in Chapter 10. Glucocorticoid therapy should be used cautiously in stomatitis unless an autoimmune disorder has been diagnosed or other causes (including infectious ones) have been ruled out.

Diseases of the Esophagus

Megaesophagus Myasthenia gravis is the most common cause of secondary megaesophagus in dogs. It is diagnosed based on response to edrophonium chloride, a short-acting anticholinesterase (Twedt, 1995). Effects on skeletal muscle occur within 1 minute of IV administration and last up to 10 minutes or longer in some myasthenic patients. Drug therapy of megaesophagus associated with myasthenia gravis targets improvement in muscular activity with anticholinesterase therapy (pyridostigmine bromide, 1–3 mg/kg orally every 12 hours) (Washabau, 1999) and suppression of the immune response with glucocorticoid or other immunosuppressive therapy (e.g., azathioprine). Pyridostigmine improves appendicular muscle strength but may not improve pharyngeal or esophageal function. Prednisone tends to be the preferred glucocorticoid but may contribute to muscle weakness. Azathioprine avoids many of the side effects of glucocorticoids, but remission takes longer to achieve (up to several weeks), and neutropenia may limit treatment. Mycophenolate mofetil is an immunomodulator used to prevent graft-versus-host rejection in human renal transplant patients. The drug inhibits purine synthesis but only in lymphocytes (both B and T lymphocytes), and side effects are limited to gastrointestinal upset. The drug can be given orally, causing response within 4 hours of administration. The drug has proved efficacious for treatment of myasthenia gravis in dogs (5–10 mg/kg every 12 hours orally) (Dewey, 2000). A prodrug, the active metabolite of mycophenolate mofetil, mycophenolic acid is currently being studied; initial clinical use appears promising. Thyroid hormone replacement (thyroxine) may also prove helpful. Treatment for megaesophagus for which an underlying cause cannot be found is difficult. A number of drugs that stimulate gastrointestinal smooth muscle have ben recommended with variable success, including metoclopramide and cisapride. Drugs that relax the lower esophageal sphincter (anticholinergics and calcium channel blockers) have not proved effective. A major focus for treatment of myasthenia gravis is prevention of aspiration pneumonia.

Esophagitis Esophagitis should be treated by correction of the underlying etiology. It is commonly associated with ingestion of a corrosive or hot (thermally) material. Antibiotic therapy in such cases should be reserved for esophageal perforation. The mucosa can be protected by administration of sucralfate administered as a slurry (1 g in 10 mL warm water), 5 to 10 mL every 6 to 8 hours. Lidocaine solution (Xylocaine viscous solution) may be administered orally (2 mg/kg every 4 to 6 hours) to minimize pain. Esophagitis caused by gastroesophageal reflux should respond well to medical management. In addition to protecting the damaged mucosa with sucralfate, drug therapy targets increasing gastric pH and tightening the lower esophageal sphincter. Antisecretory drugs (e.g., cimetidine, ranitidine, omeprazole) help to minimize damage induced by gastric acid and pepsin. Among them, nizatidine has prokinetic activity in humans comparable to that of cisapride, an effect evident within 1 hour after administration (Zarling, 1999). Interestingly, a peppermint/caraway oil preparation induced relief from dyspepsia equal to that produced by cisapride in human patients (Madish, 1999). Antacids may also prove beneficial; products containing alginic acid may provide additional protection of the esophagus by providing a barrier of foam. Prokinetic drugs should be administered in order to tighten the lower esophageal sphincter. Indeed, metaclopramide or cisapride is probably as effective as antisecretory drugs in preventing further esophageal damage associated with gastric reflux. Glucocorticoids can be used to minimize esophageal stricture formation resulting from damage to the esophagus that extends into the muscular layers. Therapy should include tapered doses of glucocorticoids followed by re-evauation at 2-week intervals.

Diseases of the Stomach

Acute Gastritis

Acute gastritis is best treated by resolution of the underlying cause, whether it is diet, infectious agents or chemicals (including drugs or toxins), or metabolic diseases (e.g., renal or liver disease). Chemicals, including hydrochloric acid and bile acids, can induce vomiting as a result of direct damage or hypertonicity. Inflammation, if allowed to progress, can result in erosion and ulceration. Although most patients with acute gastritis improve in 1 to 5 days, some patients require supportive therapy (Willard, 1995). Depending on the patient, supportive therapy (in addition to nothing given orally) may include fluid therapy, antiemetics, and protectants or adsorbents. Fluid therapy with balanced crystalloids may require the addition of potassium. Bicarbonate is rarely indicated; glucose supplementation may be indicated in some patients. Any of the antiemetics previously discussed can be used, although phenothiazine derivatives should be withheld until volume replacement has begun. Metaclopramide is useful when given either peripherally or centrally. Among the phenothiazines, chlorpromazine and prochlorperazine tend to be used most commonly (Hall, 1999). Among the protectants, bismuth subsalicylate has proved most useful in decreasing vomiting associated with acute gastritis. However, gastric distention from the drug may cause the animal to vomit; therefore prudence is indicated in its use.

Gastric Ulceration/Erosion

There is no sensitive indicator of damage to the gastrointestinal mucosa; damage may be quite extensive before hematemesis or melena is noted. Damage to the gastrointestinal mucosa (erosion or ulceration) probably occurs more frequently than anticipated. For example, up to 25% of human patients admitted to intensive care units have gastric erosions; by the third day of hospitalization, this number increases to 90%. The risk of translocation of enteric pathogens is increased in these patients, suggesting an important role for prophylactic antiulcer therapy. Sucralfate has been recommended as the preferrred method of prophylaxis in patients in whom enteral nutrition is not possible (Marino, 1997). Diseases in which mucosal damage should be anticipated and treatment implemented include but are not limited to mast cell disease, renal disease, liver disease, and inflammatory bowel disease. The underlying cause of ulceration must be resolved; additionally, antisecretory drugs and antacids are indicated for treatment of mucosal damage.

Nonsteroidal Anti-inflammatories The most commonly recognized cause of gastrointestinal ulceration in dogs is probably use of nonsteroidal anti-inflammatory drugs (NSAIDs). The primary mechanism of ulceration by NSAIDs is inhibition of the constitutive form of cyclo-oxygenase, the enzyme responsible for formation of the cytoprotective prostaglandin E. Alteration of ion (probably hydrogen) transport across the mucosa also has a variable role in ulcer formation, depending on the NSAID used (e.g., aspirin) (LaCorte, 1999). Unlike the NSAIDs, glucocorticoids impair the inducible cyclo-oxygenase enzyme; this enzyme is not necessary for generation of cytoprotective prostaglandins. Hence, glucocorticoids by themselves are much less ulcerogenic than NSAIDs. They may, however, potentiate ulceration caused by NSAIDs. Treatment of NSAID-induced gastrointestinal ulceration includes discontinuation of the drug; replacement of missing prostaglandins by administration of cytoprotectants such as misoprostol; providing cytoprotection through sucralfate; and inhibiting acid secretion by administration of an antisecretory drug (e.g., ranitidine or omeprazole). Sucralfate, misoprostol, and H_2-receptor antagonists have been studied either as sole agents or in various combinations for their ability to prevent gastrointestinal ulceration in patients requiring high doses or long-term NSAID therapy. Among them, misoprostol probably provides the most consistent protection, followed by sucralfate and then antisecretory drugs. Although famotidine was found to be equal in efficacy to misoprostol for treatment of NSAID-induced ulceration in humans (Wu, 1998), the H_2-receptor blockers are described as having only limited efficacy, particularly for ulcers in the stomach, unless it is used at higher than (generally twice) recommended doses (Brown, 1999). Proton pump inhibitors have proved superior to H_2-receptor antagonists for treatment of NSAID-induced ulceration (Brown, 1999). In cases of overdosing (including accidental ingestion), administration of both sucralfate and misoprostol is recommended along with an antisecretory drug. The duration of therapy depends in part on the elimination half-life of the drug and the amount of NSAID ingested. The elimination half-life of some of the drugs is several days, suggesting that toxic concentrations may remain in the bloodstream for some time (1 to 2 weeks). Administration of protective agents should be longer—perhaps 2 weeks or more—depending on the drug and the amount ingested. Administration of cytoprotective antacids such as magnesium/aluminum hydroxide combinations with a meal may provide further protection. Prevention of NSAID-induced ulceration in humans is best accomplished with proton pump inhibitors; omeprazole was superior to either ranitidine or misoprostol following 6 months of NSAID therapy for reducing the risk of either gastric or duodenal ulcer (Lazzaroni, 1999).

***Helicobacter* Species** The role of *Helicobacter* species as causal agents in gastrointestinal diseases in dogs and cats is being elucidated. It is likely that a causal relationship exists between the organism and the disease. In human patients, the organism is associated with gastroduodenal ulceration, inflammatory disease, and carcinoma. A causal relationship also has been suggested in ferrets, cheetahs, and cats. Clinical signs attributed to *Helicobacter* organisms in dogs and cats include chronic vomiting and diarrhea, inappetence, pica, and fever (Hall, 1999). More than 70% of human patients with gastrointestinal ulceration associated with *Helicobacter* organisms are cured of their ulcerative disease if *Helicobacter* is successfully eradicated. The pathophysiology of *Helicobacter* in part reflects urease-mediated conversion of urea to ammonia and bicarbonate. Ammonia causes local tissue damage, whereas bicarbonate appears to facilitate deeper colonization of the organism into the mucosa (Hall, 1999). Cytokine production by the organism appears to be associated with inflammation and ulcerogenesis; biochemical changes in the mucosa also contribute to disease. Treatment includes a colloidal bismuth (i.e., bismuth subsalicylate), an antibacterial that targets *Helicobacter* (metronidazole, amoxicillin, or clarithromycin), and an antacid (an H_2-receptor antagonist or omeprazole). Bismuth accumulation causes cell wall damage and subsequent cell lysis. Among the antibacterials selected, amoxicillin is associated with the greatest and clarithromycin the least amount of microbial resistance in humans. Resistance to metronidazole is also increasing. The duration of therapy in humans is several weeks. Reports of similar therapy in dogs and cats support but do not conclusively prove this approach may be beneficial in dogs and cats suffering from selected gastrointestinal diseases. One study reported marked improvement in 90% of dogs and cats treated with a combination of metronidazole, amoxicillin, and famotidine for three weeks. Sucralfate may also be of benefit.

Gastric Dilatation Volvulus Therapy for gastric dilatation volvulus (GVD) focuses on management of the acute and potentially life-threatening disease and long-term prevention. Medical management of the patient with acute disease focuses on resolution of the dilatation or volvulus and treatment of the sequelae of the syndrome. The sequelae of GVD that are most life-threatening are decreased cardiac preload (compression of the posterior vena cava and hepatic portal systems by the enlarged stomach), ischemia of the gastric wall (with loss of the mucosal barrier and increased risk of perforation), and congestion of abdominal viscera with subsequent endotoxemia and disseminated intravascular coagulation. Although they are potentially later in onset, cardiac arrhythmias also may become life-threatening. Shock should be treated with a balanced crystalloid electrolyte solution or hypertonic saline. Shock doses of glucocorticoids, or, alternatively, of flunixin meglumine (0.5–1.1 mg/kg IV) may ameliorate some of the signs or clinical sequelae of endotoxemia. Free radical scavengers (deferoxamine or allopurinol) may help reduce damage due to reperfusion. Methylprednisolone may also be helpful in minimizing the effects of oxygen radicals (see Chapter 16). Decompression of the dilated stomach can be facilitated by chemical restraint or sedation. Oxymorphone may be the drug of choice. Cardiac arrhythmias are most commonly ventricular in origin. Intravenous lidocaine is the preferred drug, administered initially as an IV bolus followed by a constant rate infusion (75 μg/kg/min). Procainamide can be used (6 to 8 mg/kg followed by 20 to 40 μg/kg/min constant rate infusion) intravenously if lidocaine is ineffective. Use of H_2-receptor antagonists to minimize the effects of hydrochloric acid on the already damaged mucosa and antimicrobials may be indicated, although their need has not been well determined.

Medical management of chronic GVD has not been well established. Motility modifiers (metaclopramide, cisapride) and H_2-receptor antagonists may be indicated, particularly after an acute episode in order to minimize the accumulation of gastric secretions. However, their efficacy has not been established.

Gastric Motility Disorders

Dietary management of delayed gastric emptying should precede pharmacologic management. Prokinetic agents can be added when dietary management fails; cisapride is preferred. Erythromycin will stimulate gastrointestinal motility at doses (0.5–1 mg/kg every 8 hours) much lower than antimicrobial doses. Among the H_2-histamine receptor antagonists, ranitidine and nizatidine inhibit anticholinesterase activity and thus are prokinetic at antisecretory doses (Hall, 1999).

Small Intestinal Diseases

Diarrhea

Acute Diarrhea Like vomiting, diarrhea should be managed by providing supportive therapy, treating symptoms, and resolving the underlying cause with specific therapy (Burrows, 1995). Generally, intestinal causes of acute diarrhea include diet, toxins or drugs, or infections (including viral, microbial, and parasitic). A number of extraintestinal diseases include diarrhea as a manifestation. For many diarrheas, rehydration and maintenance of hydration and electrolyte balance are the cornerstones of therapy (see Chapter 5). Antiemetics should be used to control vomiting. Those that cause hypotension (e.g., phenothiazine derivatives) should be withheld until fluid replacement has begun. Protectants and adsorbents are indicated for diarrheas associated with toxins (including "garbage enteritis") and may be used for nonspecific (undiagnosed) causes of acute diarrhea. Kaolin may be useful for its adsorbent properties. Bismuth subsalicylate provides both adsorbent and anti-inflammatory effects and is the preferred antidiarrheal for toxin-associated diarrheas.

Motility modifiers must also be used with discretion for treatment of diarrhea. Hypomotility rather than hypermotility is the more likely abnormality, although most motility modifiers cause hypomotility. Among the motility modifiers, opioid drugs such as loperamide are more likely to increase segmentation and thus provide resistance to outflow. Most of the motility modifiers (both opioids and anticholinergics) are more likely to be effective, however, because of their effects on electrolyte secretion (decreased) and absorption (increased) in the intestinal tract. Of the motility modifiers, the narcotic or opioid derivatives are preferred for short-term use as long as toxins, drugs, or obstruction has been ruled out. Anticholinergic motility modifiers are reserved for psychogenic causes of acute diarrhea.

Viral Enteritis

There is no specific treatment for diarrheas of viral origin. Fluid therapy, electrolyte replacement, and antiemetics are indicated, depending on the severity of clinical signs. Among the viral causes of diarrhea, canine parvovirus stands out for its severity and life-threatening nature. Supportive therapy centers around the intravenous administration of balanced electrolytes (e.g., lactated Ringer's solution) with potassium replacement. Glucose may be added when indicated by clinical signs consistent with septicemia. Damage to the mucosal barrier and risk of bacterial translocation should be treated with parenteral antibiotics. Antibiotics should target both aerobes and anaerobes. *Escherichia coli* was identified as an organism associated with septicemia in canine parvovirus (Isogai, 1989; Turk, 1990); however, *Clostridium perfringens* may also play a role (Turk, 1992). Because of the life-threatening nature of sepsis, combination therapy with a beta-lactam (amoxicillin, cephalexin) and an aminoglycoside (gentamicin, amikacin) is recommended. Vomiting and the life-threatening nature of the illness preclude oral administration of antibiotics. Ceftiofur has been used by some clinicians; however, its limited spectrum and lack of safety studies in dogs and cats should lead to caution in its use for treatment of parvovirus-associated bacteremia. In less severe infections, trimethoprim-sulfonamide and chloramphenicol may be considered. Fluorinated quinolones should be avoided if possible because of the risk of cartilage defects in young, growing animals. Because fluid therapy is likely to be intensive in these patients, increased volume of distribution should lead to higher doses of antimicrobials. Treatment of septic shock may include glucocorticoids or flunixin meglumine. These drugs can ameliorate some of the negative sequelae resulting from endotoxemia. However, their benefits are more likely to be realized within 4 hours of the onset of endotoxemia. Shock doses of glucocorticoids should be used. Controversy regarding the use of flunixin meglumine centers primarily on the risk of gastrointestinal damage. However, damage is generally so severe at the time of clinical presentation that it is reasonable to assume that the use of a single dose of flunixin meglumine is not likely to contribute to further damage. An additional benefit of flunixin meglumine is its potent visceral analgesic effect. Dogs suffering from parvovirus are often in great pain, and opioids should not be used in these patients because of their antidiarrheal effects. Flunixin meglumine can provide marked analgesia.

Although currently experimental, compounds targeting endotoxin may prove to be an important adjuvant to patients suffering from sepsis. Examples include endotoxin serum or a bacterial toxoid (*Salmonella typhimurium*; 10 mL/kg). The latter is commercially available. Transfusions with fresh whole blood or plasma can be beneficial in some dogs, particularly those that are hypoproteinemic or anemic.

Treatment of diarrhea associated with parvovirus is not indicated. Until the mucosa has had time to heal, drugs are not likley to be effective.

Bacterial Enteritis

The role of antimicrobial therapy in the treatment of diarrhea should be closely critiqued. Bacterial infection is not a major cause of diarrhea, nor does infection appear to perpetuate small intestinal diseases. More important, use of antimicrobials does not appear to improve the course of most acute diarrheas. Antimicrobials (neomycin, ampicillin) may, in fact, worsen diarrhea, perhaps because of suppression of normal microflora. Use of antimicrobials for treatment of diarrhea should be based on a diagnosis of intestinal bacterial infection (overgrowth), or in cases of mucosal damage sufficiently severe to allow bacterial translocation. In the latter case, clinical signs generally include hemorrhagic diarrhea, fever, and abnormal white blood cell counts. Systemic antimicrobial therapy is indicated for bacterial translocation.

Despite the low incidence (less than 4% of cases of acute diarrhea), bacterial infections have been associated with both acute and chronic enterotoxigenic diarrhea of both small and large intestines. Diagnosis and antibacterial treatment are best based on culture and susceptibility data when possible. Most likely therapy for each of the infecting organisms is enrofloxacin, trimethoprim-sulfonamide combinations, and chloramphenicol for *Salmonella*; erythromycin, enrofloxacin, furazolidone, doxycycline, neomycin, clindamycin, or chloramphenicol for *Campylobacter jejuni*; a prolonged course of trimethoprim-sulfonamide combinations, tetracycline, or chloramphenicol for *Yersinia enterocolitica* (prognosis is guarded); metronidazole for *Clostridium difficile*; and amoxicillin, ampicillin, metronidazole, tylosin, or clindamycin for *Clostridium perfringens* and *E. coli* (based on culture and susceptibility). Many drugs are likely to be effective, including trimethoprim-sulfonamide combinations, enrofloxacin, and chloramphenicol. *Bacillus piliformis* (Tyzzer's disease) is a less common although rapidly fatal cause of acute hemorrhagic enterocolitis. Salmon poisoning (*Neorickettsia helminthoceca* or *elkominica*) is an endemic, fatal cause of diarrhea in dogs in the Pacific Northwest. As with other rickettsial organisms, tetracycline (oxytetracycline, doxycycline) is the treatment of choice. Oral therapy (in the absence of vomiting) includes tetracycline, chloramphenicol, sulfonamides, and penicillins. Therapy should continue for 2 to 3 weeks; the trematode vector can be treated with fenbendazole for 10 to 14 days (50 mg/kg, once daily). Because bacterial infections as a cause of diarrhea are often associated with some type of toxin production, motility modifiers should

cholinergics and sedatives (e.g., chlordiazepoxide and clidinium) also may prove useful.

Enterotoxicosis associated with *Clostridium perfringens* is emerging as a cause of large bowel diarrhea primarily in dogs but potentially in cats as well. Diagnosis is based on a reverse latex agglutination test available in many human laboratories. Acute treatment includes metronidazole, ampicillin, or amoxicillin. Tylosin may be effective for cases requiring long-term treatment. High-fiber diets (or psyllium) may also be helpful. Other bacterial diseases of the large intestine were discussed as causes of diarrhea in the small intestine.

Trichomoniasis is caused by *Entamoeba histolytica* and *Balantidium coli*, protozoal organisms associated with diarrhea of the large intestine in dogs and cats. Treatment of trichomoniasis was delineated in the section on diseases of the small intestine. Treatment of amebiasis is similar to treatment of giardiasis. Treatment of *B. coli* infection has not been delineated in animals but based on the response in humans might include the use of tetracyclines or metronidazole.

Megacolon Initial medical management of megacolon associated with mild constipation should include laxatives such as bisacodyl or docusate sodium suppositories. As constipation progresses to obstipation, enemas and evacuation under general anesthesia are implemented. In severe cases, broad-spectrum antimicrobials may be indicated to decrease the potential for bacterial translocation across the damaged mucosa. Long-term medical management should be accompanied by dietary management. Laxatives and periodic enemas are indicated. Prokinetics such as cisapride have had variable success but should be tried. With the removal of cisapride from the market, prokinetic choices are limited. Erythromycin demonstrated a prokinetic effect on colonic motility but did not provide a clinically evident benefit in human patients with postoperative colonic ileus (Smith, 2000).

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is characterized by infiltration of inflammatory cells in the gastric and/or intestinal mucosa (Willard, 1995). The cause of the infiltration often cannot be identified, but it is likely that antigens to which the gastrointestinal tract are exposed (e.g., food, microorganisms, or parasites) are important in some cases. Diseases such as canine and Basenji enteropathy may appear histologically as IBD. The type of predominating cell (lymphocytic, plasmocytic, eosinophilic, or histocytic) that causes inflammation can serve as a basis of the classification—and to some degree, treatment—of IBD. Thus, proper treatment partly depends on a cytologic description of the inflammatory process. For example, eosinophilic infiltrates generally respond to dietary management alone. Unfortunately, IBD is a diagnosis of exclusion and is made after other causes of inflammatory disease of the gastrointestinal tract have been ruled out. Food allergies or intolerance, infections by fungal, bacterial, or parasitic organisms, and neoplasms must be ruled out. Associated clinical signs of IBD in cats that may require medical management include vomiting and, to a lesser degree, diarrhea. Hematochezia may be present with colitis. Diarrhea is the primary presentation of IBD in dogs. Vomiting occurs less commonly with gastric and enteric IBD; hematochezia occurs consistently in colitis. Anorexia and weight loss occur to variable degrees in IBD.

Initial medical management may vary with the severity and length of disease. In dogs, particularly, elimination of an irritating diet and antibiotic-responsive causes might be considered prior to biopsy. This is best accomplished by a well-designed clinical trial in the patient. Feeding the animal an elimination or high-fiber diet (particularly for colonic disease) might be considered first. Antibiotic therapy is intended to resolve bacterial overgrowth that might be contributing to the inflammatory process and thus be mimicking IBD. Therapy for overgrowth in the large intestine should target clostridial organisms (metronidazole or ampicillin), whereas broader spectrum drugs (tylosin, ampicillin) should be used for small intestinal disease. *Clostridium perfringens* overgrowth in the small intestine may be difficult to detect; drug therapy that targets this organism includes tylosin and ampicillin.

Use of glucocorticoids should be reserved for animals in whom biopsy has confirmed a diagnosis of IBD. Indiscriminate use of glucocorticoids can be dangerous, particularly in areas in which fungal causes of gastrointestinal disease are not uncommon. In addition, use of glucocorticoids in patients with gastrointestinal lymphoma may render the neoplasia resistant to further glucocorticoid therapy used as part of a combination antineoplastic regimen. Glucocorticoids are indicated in dogs and cats with lymphocytic-plasmacytic IBD. Prednisolone (2.2 mg/kg/day orally) should result in clinical response within 1 to 2 weeks. Therapy should continue at the same rate for another 2 weeks (beyond clinical response) and then slowly be tapered. More severe cases of IBD or cases that do not initially respond to prednisolone may respond to dexamethasone (0.22 mg/kg/day orally). The development of multidrug resistance has been implicated as a cause of therapeutic failure with glucocorticoids in some human patients with IBD; expression of mucosal multidrug resistance may ultimately be used to determine response of IBD patients to therapy (Farrell, 2000). Metronidazole therapy in conjunction with glucocorticoids is indicated not only for its antibacterial effects but also because it appears to have immunomodulatory capabilities; indeed, this may explain why it may be effective as the sole therapy in some cases of IBD.

Animals that continue to be unresponsive to medical management of IBD may respond to azathioprine (0.3 mg/kg every other day, orally in cats; 2.2 mg/kg/day in dogs). Response may take up to 5 weeks. Serum albumin levels can be used as a monitoring tool in animals with protein-losing enteropathy. Side effects of azathioprine are sufficiently severe that a diagnosis of severe IBD should be confirmed (based on biopsy) prior to its use. White blood cell counts should be monitored weekly and the drug temporarily discontinued if neutrophil counts drop below 2000/μL.

Sulfasalazine (20 mg/kg every 12 to 24 hours orally in cats; 50 mg/kg/day divided every 8 to 12 hours in dogs) may also be beneficial in cats and dogs with IBD. Response may take 1 to 2 weeks. As a sulfonamide, sulfasalazine may cause immune-mediated diseases ascribed to other

storage disease. These include D-penicillamine (10–15 mg/kg orally 30 minutes before a meal, every 12 hours; start with a lower dose and increase after the first week), and for animals that cannot tolerate D-penicillamine, trientine (2,2,2-tetramine, 10–15 mg/kg orally twice daily). In Bedlington terriers with copper hepatotoxicosis, 2,3,2-tetramine (7.5 mg/kg orally every 12 hours) may be used in lieu of trientine (and may result in greater copper elimination), but the drug must be reformulated. A more controversial treatment for copper storage disease focuses on decreased absorption of copper in the diet by treatment with zinc acetate (5–10 mg/kg or 100 mg for the first 3 months and 50 mg thereafter orally every 12 hours, 1 hour before each meal). This treatment should be started at a young age, before hepatic accumulation of copper has occurred. Monitoring plasma zinc concentrations every 2 to 3 months has been recommended to assure therapeutic concentrations and to avoid toxic concentrations of zinc that might lead to hemolytic anemia (therapeutic range of zinc is 200 to 500 μg/dL; higher than 1000 μg/dL is considered toxic).

Suppression of hepatic inflammation in chronic liver disease is problematic but critical if the progression of chronic to cirrhotic disease is to be halted. Underlying causes should be identified and removed. Hepatic damage by drugs often is reversible if the drug is discontinued before fibrosis has occurred. Drug-induced hepatic disease is often dose- and duration-dependent, meaning that the risk of toxicity increases with higher doses (plasma drug concentrations) and long-term therapy. Hence, single doses or short-term therapy with a hepatotoxic drug is not likely to lead to chronic hepatic disease. Drugs most commonly associated with chronic liver disease in dogs were discussed in Chapter 3. Anticonvulsants (primidone, phenobarbital, and phenytoin) and heartworm preventative (oxibendazole-diethylcarbamazine) are among the most commonly used drugs associated with hepatic disease.

Identifying the role of infection as a continued cause of liver disease may be difficult. However, with the exception of ascending chronic cholangiohepatitis, bacterial infection as a cause of chronic liver disease is uncommon. Because the liver is well perfused, any antimicrobial with a good gram-negative spectrum should be effective. However, as disease progresses and fibrosis deposition occurs, drugs that are more lipid-soluble should be considered (see Chapter 8).

Idiopathic chronic hepatitis (chronic active hepatitis or chronic active liver disease) is generally detected by increases in serum alanine transferase activity (greater than 10 times normal) and alkaline phosphatase activity (greater than 5 times normal). Biopsy should provide a confirmation as well as a histologic description upon which therapy and response to therapy can be based. Inflammation usually is controlled with immunosuppressant drugs; evidence of piecemeal necrosis, bridging necrosis, and fibrosis indicates their need. Prednisolone (1–2 mg/kg orally a day) should be administered until clinical remission occurs (generally 7 to 10 days) and the dose then gradually tapered (decrease every 10 days) until a minimum effective dose has been established. Clinical signs, clinical pathologic changes (at 1- to 2-week intervals), and ultimately a repeat hepatic biopsy (at 2 to 3 months) should be monitored for response to therapy. Note that glucocorticoids can increase serum bile acids, and the failure of these to decrease is not necessarily indicative of continued damage. More aggressive immunosuppressive therapy is implemented if glucocorticoids cannot be tolerated or if the progression of hepatic disease cannot be halted with glucocorticoids. Azathioprine therapy is initiated (2 mg/kg/day or 50 mg/m^2 orally given every day for 7 days, then every other day), with prednisolone therapy continued for the first 7 days and then alternated with azathioprine thereafter. Weekly white blood cell counts should be performed to detect bone-marrow suppression by azathioprine; therapy should be suspended for 5 to 7 days if the neutrophil count drops below 2000 cells/μL or the platelet count below 50,000/μL. Lymphocytic or sclerosing cholangitis/cholangiohepatitis in cats may also respond to glucocorticoid therapy (2.2 mg/kg orally a day).

Ursodeoxycholic acid has proved beneficial in both dogs and cats with chronic liver disease, particularly if it is associated with a significant cholestatic component. The dose in patients with chronic hepatitis (8 to 10 mg/kg) is less than that in patients with primary biliary cirrhosis or sclerosing cholangitis (10–15 mg/kg/day). Note that more studies are needed to describe the clinical efficacy of ursodeoxycholic acid in dogs and cats. The drug appears to be safe; cats showed no evidence of adversity when dosed with 10 mg/kg orally for 8 weeks. Dehydrocholic acid (10–15 mg/kg orally every 12 hours) has also been recommended in cats with cholangiohepatitis and "sludged bile." Note, however, that less evidence is available to support the efficacy of this bile acid and that it is among the lipid-soluble and thus potentially hepatotoxic bile acids. Ascorbic acid (25 mg/kg/day orally) has been suggested as supportive therapy in dogs with chronic hepatic disease because the liver is less able to produce this vitamin. Zinc therapy has also been suggested to reduce copper deposition in the damaged liver.

For patients in whom the progression of disease cannot be halted, and, specifically, fibrotic tissue deposition continues, antifibrotic drugs can be considered. Prednisolone provides some prevention of collagen deposition. Colchicine appears to improve (histologically) the progression of cirrhosis in human patients, but evidence is lacking in dogs because of lack of controlled trials. Adverse reactions have not been reported in dogs receiving colchicine (0.03 mg/kg/day orally) for 6 to 30 months.

Sequelae of Chronic Liver Disease

Management of gastrointestinal ulceration was previously discussed. As disease progresses, the likelihood of ulceration increases not only because of impairment of the mucosal barrier but also because of increased risk of bleeding due to coagulopathies. Bleeding into the gastrointestinal tract increases the risk of hepatic encephalopathy. Treatment of hepatic encephalopathy was discussed under acute hepatic failure.

Control of ascites can be difficult with chronic disease. Fluid accumulation is more likely to reflect increased sodium and water retention (stimulated by portal hypertension) rather than decreased albumin, although hypoalbuminemia may contribute to ascitic fluid formation. Dietary

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Drugs Affecting the Kidneys and Urination 28

Dawn Merton Boothe

RENAL PHYSIOLOGY AND DRUG THERAPY
Extracellular Fluid
Renal Transport of Fluids and Electrolytes
Atrial Natriuretic Hormone
DIURETIC THERAPY
Therapeutic Use of Diuretics
Targets of Diuretic Therapy
Principles of Diuretic Therapy Use
Factors Limiting Response to Diuretics
DIURETICS
Osmotic Diuretics
Carbonic Anhydrase Inhibitors
Thiazide Diuretics
Drugs that Interfere with Renal Epithelial Sodium Transport
Potassium-Sparing Diuretics
Aldosterone Antagonists
High Ceiling Diuretics
THE USE OF DIURETICS IN SELECTED CLINICAL CONDITIONS
Congestive Heart Failure
Cirrhosis
Nephrotic Syndrome
DRUGS THAT ALTER RENAL CONSERVATION OF WATER: ANTIDIURETIC HORMONE
DRUGS THAT ALTER URINARY pH
Urinary Acidifiers
Calcium Oxalate Urolithiasis
Urate Urolithiasis

RENAL PHYSIOLOGY AND DRUG THERAPY

Extracellular Fluid

The physiology of body fluids and the role of the kidney are also addressed in Chapters 5 and 29. The amount of extracellular fluid (ECF) present is determined primarily by total body sodium content because sodium is the major constituent of ECF and because active transport mechanisms control intracellular and extracellular compartments (Jackson, 1995). Control of ECF involves cardiovascular, renal, and central nervous systems so closely integrated that failure of one system is compensated for by another of the systems, thus ensuring that salt and water excretion remain appropriate even when changes in blood pressure occur. Compensation includes changes in renal blood flow caused by autoregulatory changes in renal efferent arteriolar resistance. Regulatory mechanisms adjust both short-term and long-term sodium and water transport rates. Thus, small increases in mean arterial blood pressure can cause a marked increase in sodium excretion, changing total body sodium (Jackson, 1995). Yet, if sodium balance becomes negative, as the sodium concentration in the ECF decreases, thirst and water intake decrease accordingly such that ECF sodium concentration normalizes. A positive balance does the opposite, resulting in an increase in water intake. These integrated systems maintain a sodium and water excretion that equals that of intake minus any lost through nonrenal mechanisms (e.g., feces, sweating).

Renal Transport of Fluids and Electrolytes

The proximal tubules are responsible for 66% of the sodium and glomerular filtrate reabsorbed by the kidney. The primary pathway of fluid and electrolyte reabsorption in the renal tubule begins in the lumen and progresses through the cell and interstitial fluid to the capillary. Two water-permeable membranes are passed during this process. In the proximal tubule, active sodium ion reabsorption from the lumen generates an osmotic gradient in the lumen that leads to an almost simultaneous movement of water into the cell. Sodium reabsorption that begins with entry across the luminal membrane continues with movement across the basolateral membrane into the interstitial space (Fig. 28–1). Basolateral movement is the energy-dependent process, fueled by an Na/K-dependent ATPase located on the basolateral membrane. The exchange rate of two K^+ for each three Na^+ entering the interstitial fluid provides an electrochemical gradient that favors passive entry of Na^+ from the lumen into the cell. The concentration gradient generated by the basolateral movement determines the rate of sodium movement from the lumen. Chloride (and to a lesser degree other anions) follow sodium, maintaining electroneutrality of the reabsorbate and a slight electronegativity of the cell compared with the luminal contents. The concentration gradient also favors passive movement of potassium from the interstitium into the cell, where it is used to continue the Na-K exchange. Although movement of sodium from the lumen into the cell is passive (albeit at the cost of an active basolateral efflux), sodium reabsorption into the cell is facilitated by three additional entry mechanisms: diffusion with chloride (quantitatively the most important), cotransport with uncharged or acidic anions, and countertransport with hydrogen ions (important to acid-base regulation and the site of carbonic anhydrase action). Although transport of sodium, water, and other electrolytes raises interstitial pressure, movement into peritubular capillaries facilitates continued reabsorption. Bicarbonate processing also occurs in the proximal tubule (see later discussion).

Unlike the proximal tubule, cells of the descending limb

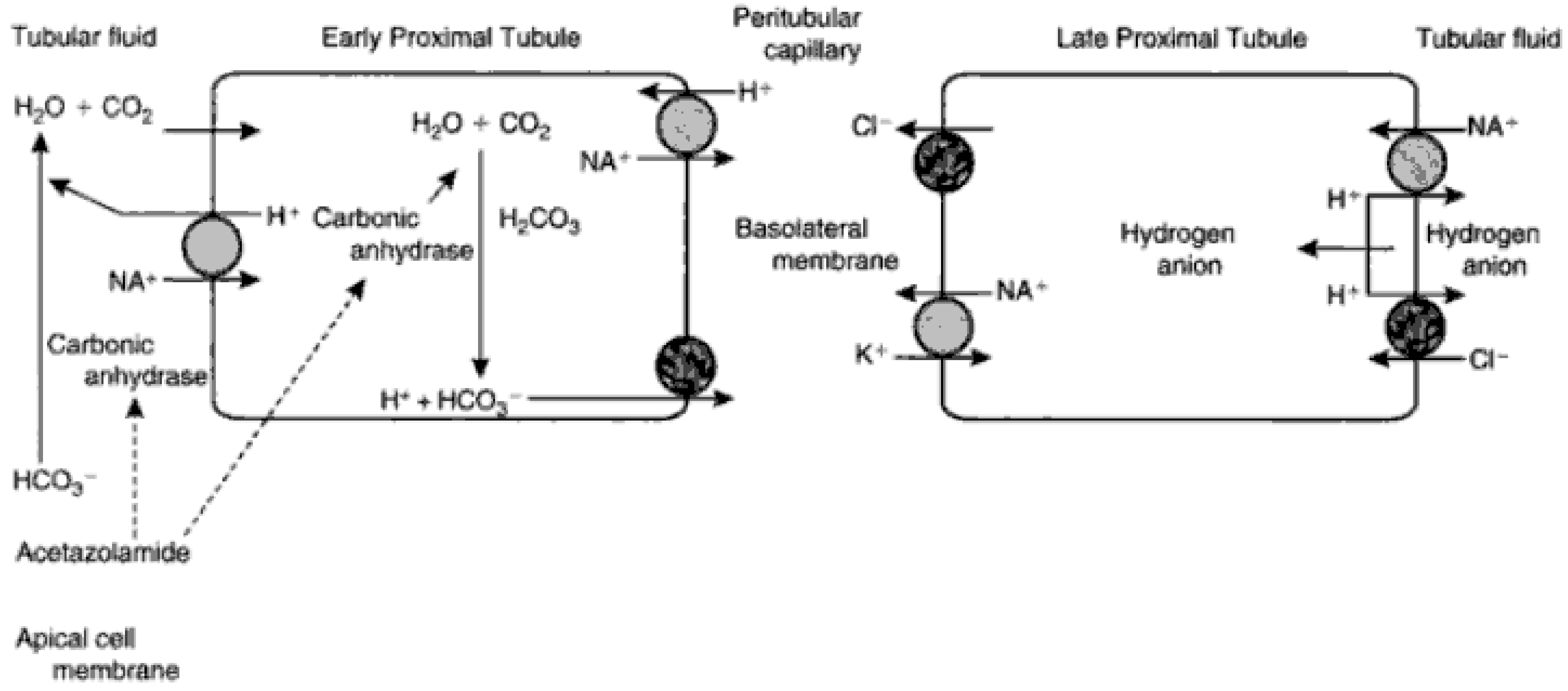

Figure 28–1. Movement of fluids and electrolytes into the proximal tubule and predominant sites of action of selected diuretics. ---- = inhibited; — = stimulated.

of the loop of Henle do not appear to be equipped with specialized transporting systems. The cells are relatively impermeable to sodium, chloride, and potassium but are permeable to water. Water moves from the lumen into the interstitium, causing electrolyte concentrations to progressively increase in the lumen until a maximum is reached at the bend. Diuretic drugs do not appear to be active in the descending portion of the tubule. In the ascending limb of the loop, chloride is transported "uphill," achieving intracellular concentrations that are higher than predicted (based on the Nernst equation) (Okusa, 1998). Chloride movement occurs by an Na (downhill), K^+-$2Cl^-$ (uphill) cotransport system, with Na^+,K^+-ATPase in the peritubular membrane providing the energy source. The high intracellular chloride concentration facilitates movement of chloride into the interstitium. The ion transports in the ascending loop of Henle are critical for proper function of the countercurrent mechanism in the renal medulla. The ascending loop of Henle tubule is not permeable to water, and fluid in the lumen becomes progressively diluted (Fig. 28–2). About 25% of sodium-chloride reabsorption and 40% of potassium reabsorption occurs in the ascending loop of Henle, although only about 15% of the filtrate is reabsorbed in this region (Okusa, 1998). In contrast to the proximal tubules, Na^+-H^+ exchange does not appear to occur in the loop of Henle, and little if any bicarbonate is processed.

Reabsorption of water and electrolytes in the distal tubule and collecting ducts is variable. Sodium and chloride are reabsorbed against a concentration gradient. Because the early distal tubule is impermeable to water, an unfavorable concentration gradient is generated that limits the effectiveness of a sodium pump. Sodium and potassium contents in the urine are closely regulated by an aldosterone-sensitive mechanism in the distal late tubule (see Fig. 28–2). Aldosterone signals the synthesis of a protein that increases the sodium and potassium permeability of the luminal membrane. As sodium moves in, potassium simultaneously moves from the interstitium into the cell. Electrogenic movement of sodium into the cell causes an electronegativity in the lumen that attracts potassium from the cell. Whether potassium is reabsorbed or excreted is determined primarily by plasma potassium, which in turn tends to depend on dietary intake (Okusa, 1998).

In the medullary collecting ducts, only small amounts of sodium chloride and potassium are reabsorbed. Antidiuretic hormone increases permeability of the cell membrane to water, which moves from the lumen, following the previously established medullary osmotic gradient. Less than 5% of filtered sodium is reabsorbed in the distal tubule and medullary collecting system (Okusa, 1998).

Atrial Natriuretic Hormone

Atrial natriuretic hormone (ANH), a "natriuretic factor" first described in 1984, is involved in the control of ECF. It is synthesized from a prohormone and stored as a peptide in granules in atrial myocardial cells. Concentrations increase above baseline when the ECF expands, blood pressure increases, or dietary salt intake increases. Renal blood flow and glomerular filtration are subsequently increased. Sodium excretion also increases, presumably by a direct tubular action. Peripheral vasodilation can result in decreased blood pressure. Effects occur rapidly but are not sustained, suggesting that ANH is a mechanism that can store equilibrium rapidly (Okusa, 1998).

Reduction of ECF is beneficial in conditions associated with inappropriate fluid retention such as selected cardiac, renal, and liver diseases. Although the cause of ECF expansion differs in each disease, the commonality is salt and water retention. Because sodium is the primary cationic constituent of ECF, sufficient renal excretion of sodium ultimately reduces ECF.

DIURETIC THERAPY

Therapeutic Use of Diuretics

Three strategies exist for movement of inappropriate fluid accumulation (edema): correction of the underlying disease

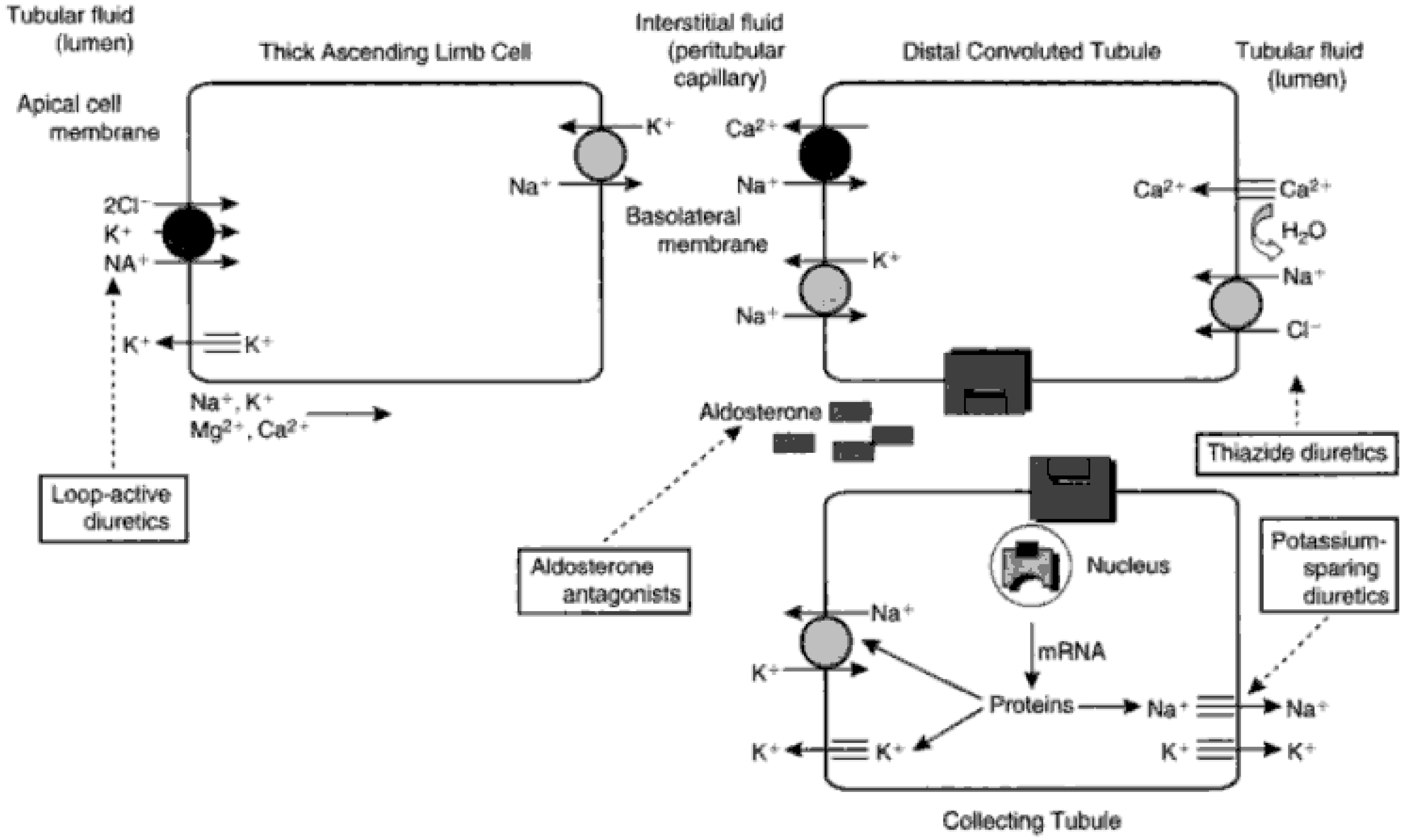

Figure 28–2. Movement of fluids and electrolytes in the thick ascending loop of Henle, the distal tubule, and the collecting ducts. The sites of action of selected diuretics are noted. The aldosterone-sensitive exchange of sodium and potassium in the late distal tubule and collecting ducts is also delineated. Like most steroidal compounds, the effects of aldosterone depend on nuclear transcription of effector proteins. ---- = inhibited; — = stimulated.

(often not possible), restriction of dietary or other sodium intake, and administration of diuretics. Of these, diuretics remain the cornerstone for treatment of edema or volume overload (Jackson, 1995). Although diuretics increase the rate of urine formation, their therapeutic indications include maintenance of urine flow; mobilization and reduction of inappropriate ECF stores such as that manifested as edema or ascites; correction of specific ion imbalances; reduction in the rate of intraocular fluid formation; reduction of blood pressure; and reduction of pulmonary capillary wedge pressure (Okusa, 1998).

Targets of Diuretic Therapy

Diuretics are classified by their mechanism of action and include the loop diuretics, carbonic anhydrase inhibitors, thiazides, osmotic diuretics, and potassium-sparing diuretics (Fig. 28–3; Table 28–1). Rational selection of diuretics relies on an appreciation of their mechanisms of action. With the exception of the osmotic diuretics and carbonic anhydrase inhibitors (the latter targets sodium bicarbonate), each class targets sodium or chloride reabsorption of tubular cells, effectively preventing the establishment of the normal ion gradient by renal tubular cells (Okusa, 1998; Jackson, 1995; Gross, 1995). Diuretics that increase net urinary excretion of sodium chloride or sodium bicarbonate also are referred to as *natriuretic*. The efficacy and use of each class of diuretics varies with their site of action and the mechanism by which sodium reabsorption is inhibited. The mechanisms vary in location within the renal tubule and include electrogenic passive diffusion (proximal and late distal tubule and collecting system); exchange with hydrogen (generated by the actions of carbonic anhydrase and bicarbonate reabsorption; proximal and late distal tubule and collecting system); cotransport with glucose, organic acids, phosphate (proximal tubule); reabsorption along with chloride reabsorption (late proximal tubule); and cotransport with chloride and potassium (thick ascending limb of the loop of Henle; results in formation of medullary interstitial hyperosmolarity).

Principles of Diuretic Therapy Use

Several principles can guide diuretic therapy (Ward, 1997): (1) The pattern of electrolyte excretion varies with the class of diuretic. (2) Maximal response is limited by the site of action of the diuretic and will be the same within a class of drugs. Thus, assuming drug delivery to the site of action has been appropriate, failure of a diuretic in one class is likely to reflect failure of another drug in the class. (3) The combination of two (or more) diuretics each from different classes (with different mechanisms of action) should cause additive and may cause synergistic effects (Okusa, 1998).

When used to reduce ECF volume, the selection of the most appropriate diuretic should be based on the cause of ECF volume retention. Diuretic selection for the patient with acute renal failure also should take into account the ability of the diuretic to reach the target tissue despite reduction in renal blood flow. The impact of the diuretic's

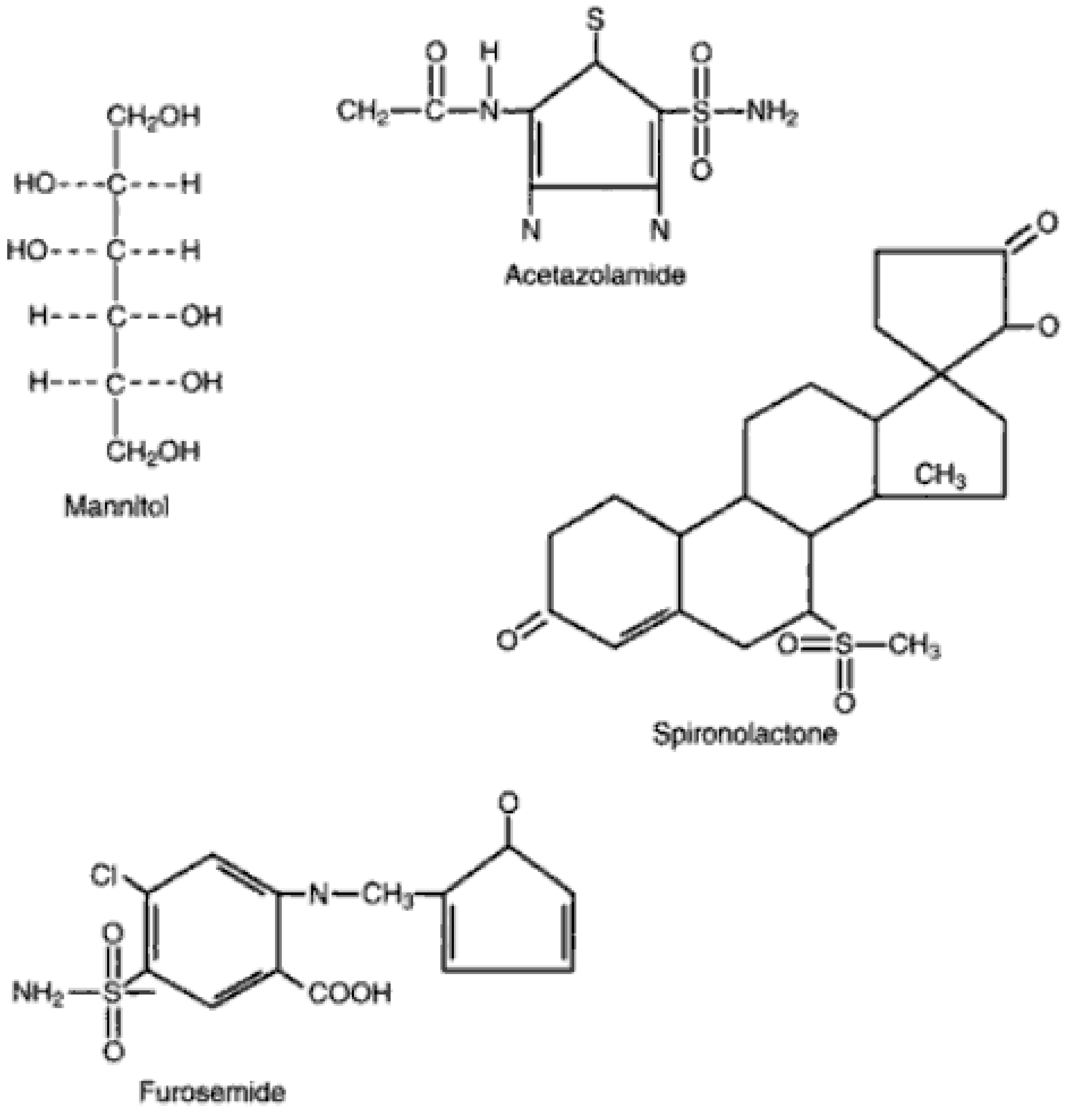

Figure 28–3. Chemical structures of selected diuretics.

direct or indirect actions on systemic sequelae beyond decreased ECF volume (i.e., metabolic acidosis, hypokalemia) should be considered. Several diuretics also influence renal physiology by virtue of their effects on renal vasculature and may be preferred during states of reduced renal blood flow. Finally, several diuretics target physiologic processes that are not unique to the kidney (i.e., carbonic anhydrase inhibitors) and thus may be used therapeutically for reasons other than diuresis.

Factors Limiting Response to Diuretics

Two types of tolerance to diuretic therapy have been described in human patients. Short-term tolerance, or "braking," occurs after the first dose and probably reflects a response to protect intravascular volume. Restoration of diuretic-induced loss of volume will resolve this type of tolerance. Long-term administration of loop diuretics can cause tolerance that reflects hypertrophy of the distal nephron in response to prolonged exposure to increased solute concentration. Sodium reabsorption increases accordingly, decreasing diuresis. Because thiazides target regions of the nephron that hypertrophy, a combination of thiazides with loop-acting diuretics results in a synergistic diuretic response in some human patients.

Several other factors may negatively impact response to diuretic therapy. Most diuretics are present at physiologic pH as uncharged molecules or organic ions and reach the renal tubular cell by active tubular secretion. The degree of ionization can impact the rapidity with which drugs are transported to renal receptors. Declining renal blood flow can preclude drug delivery to the site of diuretic action. For drugs that must reach distal sites (e.g., thiazides), doses may need to be doubled in order to achieve a clinical response. For each diuretic, a threshold (in drug concentration) must be reached before diuresis will occur. Lack of response may reflect simply an underdose for that patient, and dose titration is indicated. With renal disease characterized by proteinuria, many diuretics will remain bound to plasma proteins present in the tubular lumen and thus will remain inactive. Administration of the diuretic with albumin appears to facilitate response to diuretics in human patients with edema associated with the nephrotic syndrome. Resistance to diuretic therapy also may reflect the presence of another drug that decreases response. For example, nonsteroidals can alter intrarenal prostaglandin regulatory mechanisms, and a number of drugs compete for active tubular secretion of the diuretic into the tubular lumen.

In addition to their direct tubular effects, all diuretics indirectly influence renal tubular function. Accommodation to the effects of a diuretic in a normal animal may result in the loss of any pharmacologic effect several days after the start of diuretic therapy. Response to any diuretic will be modulated by internal homeostatic mechanisms that normally direct body fluid volumes and osmolar concentrations. For example, if a diuretic fails to cause a net sodium excretion (such as occurs with mannitol), ECF contraction will increase the concentration of electrolytes, stimulating water intake and replenishment of the lost volume (Okusa, 1998). Refractoriness to thiazides can develop rapidly due

to activation of salt-retaining mechanisms. Edema (ascites) associated with liver disease may not respond to diuretic therapy because signals from the cirrhotic liver indicate a depleted rather than exaggerated ECF (Okusa, 1998).

Finally, refractoriness to diuretic therapy may reflect pharmacokinetic changes. The oral bioavailability of some diuretics (e.g., furosemide) is quite variable in human patients and unpredictable in the individual patient. Several different doses may need to be tried before the most effective is found. Some diuretics (spironolactone, amiloride) are more effective after metabolism by the liver. Although the elimination half-life of several diuretics is sufficiently long to allow twice daily elimination (in human patients), several of the loop diuretics are characterized by an elimination half-life of 2 to 3 hours. For such drugs, the pharmacologic effect is decreased once the drug is no longer present. Rebound reabsorption of sodium by the nephrons has been described in such cases, suggesting that constant intravenous (IV) infusion may provide better response. In addition, in patients that are not responding well, small increases in diuresis in the presence of the drug potentially will be magnified to clinically significant increases if the response is continuous.

Refractoriness to diuretic therapy can be approached by cage rest (which may improve renal circulation), an increase in the dose of the diuretic, IV administration, the use of a more effective diuretic (such as a loop-active diuretic), or a decrease in interval such that the drug is present at the site for a longer period of time (constant infusion). For constant IV infusion, a loading dose (full to double dose) should be given followed by a maintenance dose given each hour (Table 28–2). Continued refractoriness should lead to the addition of a second diuretic that works through a different yet complementary mechanism of action (e.g., thiazides with a loop-acting drug).

DIURETICS

Osmotic Diuretics

For a solute to act as an osmotic diuretic, it must be freely filtered at the glomerulus, not be reabsorbed by the renal tubule, and be pharmacologically and metabolically inert. Mannitol is the most commonly used osmotic diuretic; others include urea, glycerol, and isosorbide. As the concentration of an osmotic diuretic increases in the renal tubular lumen, osmotic forces overcome the movement of water with sodium into the renal tubular cell. Eventually, as water retention in the urine increases, sodium concentration decreases and passive sodium reabsorption is reduced. Sodium loss is, however, relatively small. Although mannitol appears to work throughout the renal tubule, the principal site of action appears to be the loop of Henle (Jackson, 1995). Mannitol is distributed to ECF and thus extracts water from intracellular compartments, increasing ECF, decreasing blood viscosity, and inhibiting renin release (Jackson, 1995). Renal blood flow increases, removing NaCl and urea from the renal medulla and decreasing renal medullary tonicity. Medullary tonicity also may be reduced further by a prostaglandin-mediated increase in renal medullary blood flow. Mannitol is not absorbed after oral administration. In humans, it is characterized by an elimination half-life of approximately 1 hour.

The major adverse effect of osmotic diuretics is increased ECF, which can be detrimental in patients with pulmonary edema or cardiac failure. Hyponatremia resulting from water extraction causes headaches, nausea, and vomiting in human patients (Jackson, 1995). In contrast, loss of water in excess of electrolytes can cause hypernatremia and dehydration. Osmotic diuretics generally are contraindicated in anuria of severe renal disease or in patients that are not responsive to test doses. Mannitol and urea also are contraindicated for patients with active cranial bleeding. Glycerin (but not mannitol) can be metabolized, causing hyperglycemia.

Mannitol is most commonly used to treat acute renal failure resulting from an acute reduction in glomerular filtration or acute changes in renal tubular permeability. Mannitol provides protection to the tubules in that it attenuates reduction in glomerular filtration rate (GFR) associated with acute tubular nephrosis if the drug is administered before an ischemic insult (Jackson, 1995). Efficacy (experimentally), however, is documented only when administered before the toxin; clinical efficacy is less obvious. Mannitol is particularly indicated for treatment of toxic nephrosis because the concentration of the toxin in the urine will be reduced by the osmotic draw of water by the solute. In contrast to diuretics that act on tubular segments, osmotic diuretics usually maintain their effect in the oliguric state that accompanies acute renal failure because they will continue to be filtered by the glomerulus. If the tubular cell becomes permeable, however, as may occur with certain toxins, or prolonged tubular ischemia, the osmotic diuretics may lose their efficacy. Yet in patients with acute tubular nephrosis, mannitol may convert an oliguric patient to a nonoliguric state (Jackson, 1995).

Mannitol is distributed to ECF and thus is not effective in movement of fluids from interstitial tissues. Extracellular fluid volume will initially increase and may prove detrimental to the patient with decompensated cardiac function. Plasma osmolality increases after treatment with mannitol. Cerebrospinal fluid (CSF) and aqueous humor formation subsequently decrease. Intracellular edema will also be reduced; hence mannitol is used to treat selected causes of cerebral edema associated with increased intracellular fluid volume. Mannitol can be used to decrease brain mass before neurosurgery.

Carbonic Anhydrase Inhibitors

Two types of carbonic anhydrase are located in the proximal tubule, both targeted by carbonic anhydrase inhibitors: type II, located in the cytoplasm; and type IV, located in the luminal and basolateral membranes (see Fig. 28–1). In the lumen, H^+ (generated from the Na^+-H^+ transporter) reacts with HCO_3^- to form H_2CO_3, which, in the presence of brush border carbonic anhydrase, rapidly decomposes to water and CO_2. The CO_2 rapidly diffuses into the tubular cell, where it reacts with water to form H_2CO_3. This reaction normally proceeds slowly but is markedly accelerated by carbonic anhydrase in the cytoplasm. Because intracellular H^+ is low (due to Na^+-H^+ cotransport), H_2CO_3 spon-

result from both the direct effects and the development of metabolic acidosis. Although carbonic anhydrase also is located in the gastric mucosa, only large doses of inhibitors reduce gastric acid secretion. Carbonic anhydrase activity in red blood cells will be impaired, causing an increase in CO_2 levels in peripheral tissues and decreased levels in expired air. Carbonic anhydrase can increase delivery of solutes to the macula densa. Tubuloglomerular feedback may be triggered, increasing afferent arteriolar resistance and reducing renal blood flow and GFR.

Side effects of carbonic anhydrase inhibitors are not common. Large doses may cause drowsiness. Because they are sulfonamide derivatives, side effects typical of sulfonamides can occur. Side effects can also occur due to urinary alkalinization or metabolic acidosis. Hepatic encephalopathy can be induced as renal ammonia is diverted from the urine. Precipitation of calcium phosphate may cause calculus formation. Respiratory or metabolic acidosis can be worsened. Carbonic anhydrase inhibitors are contraindicated in patients with cirrhosis or other causes of hepatic encephalopathy or conditions associated with acidosis. The impact of carbonic anhydrase inhibitors on urinary pH can reduce the rate of excretion of weak bases (Jackson, 1995).

Acetazolamide is a potent, reversible inhibitor of carbonic anhydrase. Its primary indication in veterinary medicine is for the treatment of glaucoma with the intent to decrease aqueous humor formation. It is used less commonly to control CSF formation in patients with hydrocephalus or other causes of increased cerebral fluid pressure. Acetazolamide is characterized by some antiepileptic activity, although tolerance rapidly develops to this effect. Occasionally, acetazolamide might be used to alkalinize the urine. Indications might be for selected causes of crystalluria and to facilitate excretion of weakly acidic drugs, such as phenobarbital, and salicylate. Because its efficacy is self-limiting, combination with sodium bicarbonate may be indicated if persistent urinary alkalinization is desired.

Acetazolamide is orally bioavailable, with peak concentrations occurring within 2 hours after administration. The drug is eliminated by active tubular secretion with some passive reabsorption. In humans, the drug is totally eliminated in 24 hours. The drug is relatively safe, although metabolic acidosis may occur but is usually self-limiting. In patients with hepatic encephalopathy, alkaline urine may increase the amount of urinary ammonia reabsorbed because a greater proportion will be un-ionized. This may result in exacerbation of neurologic dysfunction, and this drug should not be used for the patient with severe hepatic dysfunction. Acetazolamide decreases iodide uptake by the thyroid gland (perhaps similar to other sulfonamide antibiotics) and should be avoided in hypothyroid patients or patients undergoing thyroid testing. Whether the drugs can render a euthyroid patient hypothyroid is not known. Drugs that depend on urine acidity are less effective when used with acetazolamide. This includes urinary antiseptics such as methenamine, which is rarely if ever indicated in veterinary medicine; efficacy of weakly acidic antibiotics might also be impaired whereas that of weak bases will be enhanced.

Thiazide Diuretics

The thiazide diuretics, represented by chlorothiazide, were developed to enhance the potency of carbonic anhydrase inhibitors (Jackson, 1995). Although most do inhibit carbonic anhydrase to some degree, their efficacy as diuretics reflects their ability to directly inhibit sodium chloride cotransport in the distal tubule, perhaps by competing with chloride for binding (Jackson, 1995). Newer diuretics have been developed that act at the same site as the thiazides, but are not thiazides; the term *thiazide-like diuretics* is applied to these latter drugs. The primary site of action is the distal tubule (a site characterized by avid binding for thiazide diuretics). Although some action has also been described in the proximal tubule, this may reflect the weak carbonic anhydrase action of these drugs. Compared with other diuretics, the thiazide diuretics are less effective in causing sodium excretion because close to 90% of reabsorption of sodium from the urine has occurred by the time the distal tubule is reached. Because the tubular site of potassium secretion is distal to the site of thiazide action, potassium excretion is increased, and more sodium is reabsorbed. Thiazides have variable effects on calcium excretion, with excretion *decreasing* with chronic administration. Thiazides cause magnesium excretion, and the potential advent of hypomagnesia is being recognized in humans receiving thiazides long term (Jackson, 1995).

The thiazides vary in their oral bioavailability, with that of chlorothiazide being the poorest (10% bioavailable in humans). Likewise, the elimination half-life of the drugs is also variable, with that of chlorothiazide being very short (1.5 hours in humans). For hydrochlorothiazide, bioavailability (in humans) is 65%, whereas the elimination half-life is 2.5 hours. Thus, the duration of diuretic effect is quite variable. The potency also is variable, with chlorothiazide 10 times more potent than hydrochlorothiazide. Thus, doses also are quite variable. The degree of protein binding varies among the drugs, and thus delivery to the kidneys via glomerular filtration may be limited. Active tubular secretion of the drugs can be antagonized by probenecid.

The thiazide diuretics are characterized by a wide safety margin, and clinical toxicity is rare. As with the loop diuretics, most serious toxicities reflect overzealous use. Volume depletion, hypotension, hyponatremia, hypochloremia, hypomagnesemia, and *hypercalcemia* have been reported. Potassium depletion can be clinically significant, particularly in patients with primary or secondary hyperaldosteronism. Oral potassium supplementation is indicated for patients that become hypokalemic; this is particularly important for patients receiving digoxin because the risk of digoxin toxicity is enhanced in the hypokalemic patient. Alternatively, the thiazides can be used in combination with a potassium-sparing diuretic. Like the carbonic anhydrase inhibitors, thiazides may exacerbate neurologic dysfunctions associated with cirrhotic liver disease. Thiazides appear to diminish the effects of insulin, particularly in the hypokalemic patient, and should not be given to patients with diabetes mellitus.

Thiazides are involved in a number of drug interactions. They can diminish the effectiveness of anticoagulants, uricosuric drugs (for treatment of gout), and insulin and may increase the effects of anesthetics, digitalis glycosides, lithium, and vitamin D. Thiazides do provide additive or synergistic effects when combined with loop diuretics. Efficacy of the thiazides is decreased by nonsteroidal anti-inflammatory drugs and methenamines (due to alkaliniza-

mer perhaps due to attenuation of response to renal prostaglandins and the latter to competition for active tubular secretion. In contrast, the thiazides act synergistically with furosemide to induce diuresis. The nephrotoxic potential of other drugs (e.g., cephalosporins, aminoglycosides) is enhanced by furosemide. Patients that are allergic to sulfonamides may show a cross reactivity to furosemide.

Furosemide is used for a variety of indications (see Table 28–1). Note that its use for treatment of hypertension is limited to animals that have not responded to other therapies. Furosemide is used for a large number of causes of edema. It is the drug of choice for the management of acute pulmonary edema. Its use in the long-term management of sodium retention might be postponed until other, less effective diuretics become ineffective. Edema associated with the nephrotic syndrome appears to respond only to loop diuretics. For the patient with refractory edema, furosemide can be combined with other diuretics, preferably one that is potassium sparing such as the thiazides or spironolactone. Doses much higher than normal may be necessary to induce diuresis in patients with renal disease for two reasons. First, renal tubular function is abnormal, and response to furosemide may be impaired. Second, drug delivery to the site of action may be decreased. Proteinuria due to glomerular nephritis may also reduce the efficacy of furosemide because it binds to protein in the urine. The massive doses necessary for acute renal failure may cause hepatotoxicity. Once oliguria has been definitively established, furosemide therapy should be discontinued. Because loop diuretics interfere with the kidney's ability to produce a concentrated urine, when combined with hypertonic saline, furosemide can be used to treat life-threatening hyponatremia.

THE USE OF DIURETICS IN SELECTED CLINICAL CONDITIONS

Congestive Heart Failure

The intial diuretic selection for human patients with mild congestive heart failure is a thiazide; however, most patients will require a loop diuretic. In human patients, the rate of oral absorption of diuretics is slowed, requiring longer to maximal response. Delivery of loop diuretics to their site of action is normal, and doses do not necessarily need to be increased unless there is evidence of renal insufficiency. Renal response to diuretic therapy may be decreased, however, requiring more exposure to drugs. Although a dose increase may be indicated, a decrease in interval may be more likely to cause a response. A thiazide diuretic should be added to therapy if dietary salt retention coupled with a loop diuretic have not been effective. Attention should be paid to ensure that hypokalemia and volume depletion do not occur with this combination. The use of spironolactone may increase as its effects on cardiac remodeling are further described.

Cirrhosis

Ascites that accompanies cirrhotic liver disease generally reflects a state of hyperaldosteronism and subsequent sodium and water retention. As such, in human patients, spironolactone is the diuretic of choice. Although the amount of diuresis can be expected to be only moderate, this is desirable because greater diuresis may negatively impact intravascular volume. In human patients, repeated large-volume paracentesis minimizes the need for more potent diuretics. The active metabolites of spironolactone allow once daily dosing, although 3 to 4 days must elapse before full pharmacologic effects are realized. Insufficient response to spironolactone indicates the need for an additional diuretic; spironolactone should be continued. For human patients, a thiazide is used initially, and a loop diuretic is used in place of the thiazide only if response has been inadequate. The decreased response to a loop diuretic in a patient with cirrhosis is not understood but does not reflect decreased drug delivery. Rather, the tubular cells do not respond maximally. Although higher doses may be of benefit, decreasing the interval may be more likely to increase response.

Nephrotic Syndrome

Response to diuretics in patients with the nephrotic syndrome may be less than ideal if hypoalbuminemia is sufficient to decrease binding of the diuretic (e.g., <2 g/dL). Unbound drug will diffuse into tissues (i.e., volume of distribution will increase), removing the drug from the site of action in the renal tubule. In such patients, addition of albumin to the therapeutic regimen will increase response. Binding to albumin in tubular fluid also decreases response and is more likely to occur when urine albumin concentrations exceed 4 g/dL. Dose increases (twofold to threefold) may help compensate for increased tubular binding of the diuretic. Because tubules in patients with nephrotic syndrome may not respond as well as those in the normal patient, decreasing the interval also may increase response.

DRUGS THAT ALTER RENAL CONSERVATION OF WATER: ANTIDIURETIC HORMONE

Antidiuretic hormone (ADH) is released by the posterior pituitary in response to increased plasma osmolality (as little as 2%, or 280 mOsm/kg) and depleted ECF volume (e.g., acute causes such as hypovolemia, sodium depletion, and hemorrhage, and chronic causes such as cardiac failure, hepatic cirrhosis with ascites, hypothyroidism, and excessive use of diuretics). Antidiuresis involves the hypothalamus, neurohypophysis, posterior pituitary, and kidney. Neurons of osmoreceptors, baroreceptors, and higher cerebral centers stimulate the hypothalamus. Calcium-mediated degranulation results in the release of ADH as well as oxytocin and other mediators. A number of chemical mediators are also associated with the release of AHD, including angiotensin II, prostaglandins, and acetylcholine. Inhibitors of release include opioids, atrial natriuretic peptide, and γ-aminobutyric acid.

The actions of ADH are receptor mediated. At least two receptors have been identified. Both receptors are located in the kidney, although the specific tissue site varies. Glomerular, vasa recta, and interstitial medullary receptors

29 Treatment of Urinary Disorders

India F. Lane

- MANAGEMENT OF ACUTE RENAL FAILURE
- Pathophysiology
- General Considerations in Management
- Fluid Therapy
- Methods to Enhance Urine Production
- Management of Hyperkalemia and Metabolic Acidosis
- Maintenance Fluid Therapy
- Other Considerations
- Cellular Protectants
- MANAGEMENT OF CHRONIC RENAL FAILURE
- Pathophysiology
- Dietary Strategies
  - Protein
  - Phosphorus
  - Sodium
  - Lipids
  - Energy
- Dietary Supplements
  - Phosphorus Binders
  - Alkalinizers
  - Potassium
- Summary of Dietary Recommendations
- Management of Anorexia and Vomiting
- Management of Systemic Hypertension
- Management of Secondary Hyperparathyroidism
- Management of Anemia
- MANAGEMENT OF GLOMERULAR DISEASE
- Pathophysiology and General Considerations
- Glomerulonephritis
- Renal Amyloidosis
- DIALYTIC THERAPY
- RENAL TRANSPLANTATION
- MANAGEMENT OF MICTURITION DISORDERS
- Physiology of Micturition
- The Hypocontractile Urinary Bladder
- The Hypercontractile Urinary Bladder
- The Hypotonic Urethra
  - Reproductive Hormones
  - α-Adrenergic Agonists
- The Hypertonic Urethra (Functional Urethral Obstruction)
  - α-Adrenergic Antagonists
  - Striated Muscle Relaxants
- DRUGS USED IN THE MANAGEMENT OF FELINE LOWER URINARY TRACT DISEASE
- Urinary Acidifiers
- Urinary Antiseptics
- Glucocorticoids
- Antispasmodic Agents
- Miscellaneous Agents
- INTRAVESICULAR AGENTS USED IN LOWER URINARY TRACT DISEASE
- Miscellaneous Agents
- Dimethylsulfoxide
- Bacillus Calmette-Guérin Therapeutic
- Piroxicam

MANAGEMENT OF ACUTE RENAL FAILURE

Pathophysiology

Acute renal failure results from a sudden, severe decline in renal function, which may be initiated by prerenal, renal, or postrenal causes. Although several specific renal diseases can cause acute renal decompensation, in veterinary medicine acute *intrinsic* renal failure is most commonly caused by a nephrotoxicant or an infectious or ischemic injury. The proportionately high blood flow and large capillary surface area in the kidney increase the organ's sensitivity to blood-borne toxicants. Additionally, the sophisticated transport mechanisms, intensive metabolic activity, and refined concentrating mechanisms found in renal tubules increase the likelihood of toxic injury. Glomeruli, too, are susceptible to direct destruction and immunologic injury. The most common nephrotoxicants encountered in veterinary medicine are ethylene glycol and therapeutic agents such as aminoglycosides, amphotericin B, cisplatin, radiographic contrast agents, and analgesics.

Ischemic injury may result from any insult that compromises perfusion of afferent arteriolar blood flow. Hypoperfusion from shock, dehydration, or hypotension is the most common mechanism of renal ischemia. Trauma, anesthesia, cardiac output failure, and persistent vomiting or diarrhea are potential ischemic events encountered in small animals. Thrombosis, hyperviscosity, and polycythemia are additional, less common disorders that interfere with renal blood flow. Angiotensin-converting enzyme (ACE) inhibitors (captopril, enalapril, lisinopril), widely used in the management of congestive heart failure in dogs, inhibit production of the vasopressor angiotensin II. In the glomerulus, angiotensin II blockade preferentially dilates efferent arterioles, which may lead to loss of glomerular capillary pressure and reduction in glomerular filtration (see Chapter 30). The vasodilatory effect is most prominent in diseased or poorly perfused kidneys and can lead to progressive azotemia or overt acute renal failure in treated patients (Toto, 1994; Longhofer et al., 1993).

The administration of nonsteroidal anti-inflammatory agents (NSAIDs) may inhibit vasodilatory prostaglandin production in the kidneys. The effect of NSAIDs is minimal in healthy kidneys but can be devastating when superimposed on marginally functioning kidneys, hypovolemia, or other vasoconstrictive states (anesthesia, surgery, sepsis, heart failure, liver failure, nephrotic syndrome) (Murray and Brater, 1993). In these disorders, renal blood flow and glomerular filtration rate become increasingly dependent on prostaglandin synthesis; administration of NSAIDs can precipitate renal ischemia and failure. Many systemic diseases increase the risk of acute renal failure by ischemic or vascular mechanisms. These disorders include pancreatitis, hepatic failure, heat stroke, disseminated intravascular coagulopathy, rickettsial disease, and bacterial endocarditis (Forrester and Lees, 1995).

Both toxicant and ischemic insults to nephrons lead to impairment of cellular transport mechanisms, cellular swelling, and death. Cellular hypoxia and intracellular calcium overload lead to additional membrane damage and oxygen free radical formation. Vascular congestion and tubular obstruction result from cellular swelling and act as common mechanisms perpetuating renal ischemia and renal failure (Lane et al., 1994). Therapeutic measures employed in acute renal failure attempt to support renal excretory function, attenuate cellular damage, and favor renal recovery.

General Considerations in Management

Goals of management of established acute renal failure are to (1) treat or minimize underlying disease processes; (2) correct fluid, electrolyte and acid-base disorders; (3) initiate a diuresis; (4) manage systemic complications; and (5) establish a prognosis (Wood, 1997; Okusa, 1998). The first principle in managing any disease process is to "treat the treatable." In acute renal failure, "treatable" problems may include dehydration or hypovolemia, postrenal obstruction, cardiac or hepatic disease, leptospirosis, rickettsial disease, bacterial endocarditis, pyelonephritis, hypercalcemia, renal lymphoma, and hemoglobinuria. Early recognition of potential toxicant-induced renal failure allows for treatment with specific antidotes (e.g., 4-methylpyrazole or ethanol for ethylene glycol) or with nonspecific measures such as gastric lavage, fluid therapy, and cathartics. Administration of any potentially nephrotoxic agents should be stopped.

Fluid Therapy

After identification of underlying disorders, the management of acute renal failure relies largely on management of fluid, electrolyte, and acid-base imbalances. Fluid deficits are estimated (estimated percentage dehydration × body weight in kilograms = liters required) and replaced rapidly, within 4 to 6 hours. Initial fluid choices include 0.9% saline or other replacement solutions. Low sodium fluids such as 0.45% saline/2.5% dextrose or half-strength lactated Ringer's solution in 2.5% dextrose may be utilized for patients with cardiac insufficiency or hypernatremia. Fluids for maintenance requirements (40 to 60 mL/kg per day) and ongoing losses (polyuria, vomiting, diarrhea) should be added to the daily fluid total. In most cases, rehydration fluid requirements will equal two to three times maintenance requirements; careful calculation of deficits and ongoing needs is recommended to prevent underestimation of fluid needs (Table 29–1).

Urine output should be measured during the rehydration phase to document appropriate diuresis and to calculate future fluid requirements. After adequate volume replacement, urine output should reach at least 1 to 2 mL/kg per hour. Oliguric patients, in which urine output is less than 1 mL/kg per hour, require additional treatment. If the animal is not overhydrated, mild volume expansion may be considered. Administration of an additional 3% to 5% of the animal's body weight in fluid should eliminate any remaining, undetected volume deficits and enhance renal perfusion and glomerular filtration rate (GFR) (Chew, 1992). If volume expansion is attempted, the patient must be carefully monitored for signs of overhydration, including increased bronchovesicular sounds, tachycardia, restlessness, chemosis, and serous nasal discharge. Appropriate volume expansion is documented by a modest increase in body weight and modest reductions in the hematocrit and plasma protein concentrations.

Methods to Enhance Urine Production

If urine production remains poor after rehydration and volume expansion, pharmacologic manipulation of oliguria is warranted. Furosemide, dopamine, and osmotic diuretics are options (see Chapter 28 and, for dopamine, Chapter 30). Furosemide (2 to 3 mg/kg intravenously [IV] every 6 to 8 hours) is often chosen as an initial treatment for oliguria because it is readily available and easy to administer. A constant rate infusion of furosemide (1 mg/kg per hour) has also been recommended (MacIntyre and Royer, 1995; Chew, 2000). As a loop diuretic, furosemide helps increase tubular flow and improve renal blood flow but does not significantly affect GFR (Lane et al., 1994). It is also speculated that furosemide's activity may protect cells of the thick ascending loop of Henle by reducing active transport at this site. Furosemide has been shown to exacerbate gentamicin toxicity and should be avoided in patients recently treated with aminoglycosides (Adelman et al., 1979). If urine output does not increase within 30 to 60 minutes, furosemide may be repeated at 4 to 6 mg/kg IV at 30- to 60-minute intervals; concurrent dopamine administration should also be considered. Volume and potassium requirements should be carefully addressed during furosemide treatment.

The efficacy of furosemide in reversing oliguria appears to be improved with the concurrent administration of dopamine (Lindner et al., 1979). Dopamine is a catecholamine (a norepinephrine precursor) that, in low doses, causes increases in renal blood flow. In dogs, dopamine acts at specific splanchnic and renal receptors to cause efferent arteriolar vasodilation, enhancing renal blood flow and sodium excretion. Dilation of mesenteric, coronary, and intracerebral vascular beds also is expected. Effects on GFR are modest (Denton et al., 1996). In cats, dopamine appears to stimulate α-adrenergic receptors, leading to increased blood pressure and natriuresis (Clark et al., 1991). Dopamine must be administered as a constant rate infusion, ideally with an automated fluid infusion pump. Dopamine is administered diluted in nonalkaline fluids, usually normal saline or dextrose solutions. Infusion rates of 1 to 5 μg/kg per minute are recommended. Infusion is usually started at 1 to 2 μg/kg per minute while the patient is monitored for changes in heart rate or rhythm. Tachycardia, ectopic or premature ventricular beats, nausea, vomiting, and hypertension are adverse effects, predominantly seen at higher doses. The pressor effects of dopamine are variable and can be detrimental to renal function; monitoring of urine output and degree of azotemia is imperative in individual patients. The half-life of dopamine is approximately 2 minutes; effects are withdrawn within 10 minutes after the infusion is discontinued. The drug is metabolized to inactive compounds by monoamine oxidase and catechol-O-methyltransferase in the kidney, liver, and plasma (Plumb, 1995). Fenoldopam and other new selective dopamine subtype DA-1 receptor agonists may more effectively increase renal blood flow in dogs (Chew, 2000). Neither dopamine

Table 29–1. Drugs Used in the Management of Acute Renal Failure

Agent	Actions	Dosage	Adverse Effects	Contraindications
Agents Used to Enhance Urine Production				
Furosemide	Loop diuretic ↑ RBF	2–3 mg/kg IV q6–8h 2–6 mg/kg IV q30–60 min 1 mg/kg/h IV CRI	Volume depletion, hypokalemia	Gentamicin, nephrotoxicity
Dopamine	↑ RBF, ↑ GFR ↑ Natriuresis	1–5 μg/kg/min IV CRI	Arrhythmias, hypertension, vomiting	
Mannitol	Osmotic diuresis ↓ Cellular edema Free radical scavenger	0.5–1.0 g/kg IV slow bolus (10%–20% solution)	Pulmonary edema, GI upset	Overhydration, cardiac disease
10%–20% Dextrose	Osmotic diuresis Caloric support	25–50 mL/kg IV slow infusion q8–12h	Volume expansion, hyperglycemia, hyperosmolality	
Agents Used to Treat Hyperkalemia				
Calcium gluconate (10% solution)	Cardioprotection	0.5–1.0 mL/kg IV slow bolus	Arrhythmias	
Sodium bicarbonate	Alkalinization of ECF	0.5–2 mEq/kg IV slow bolus	Hypernatremia, ↓ ionized calcium, hypokalemia	Hypocalcemia
Dextrose	↑ Insulin	0.1–0.5 g/kg IV (1–2 mL/kg 25% solution)	Hyperglycemia, hyperosmolality	
Insulin/dextrose	Intracellular movement of potassium	0.25–0.5 U/kg insulin *with* 1–2 g dextrose per unit insulin given	Hypoglycemia	
Agents Used to Treat Metabolic Acidosis				
Sodium bicarbonate	Alkalinization	See text for dosage information	Hypernatremia, hypokalemia, ↓ ionized calcium	
Agents Used to Treat Nausea/Vomiting				
Cimetidine	H_2 antagonist	2.5–5.0 mg/kg IV q8–12h	Altered drug metabolism	Severe renal or hepatic failure
Ranitidine	H_2 antagonist	2 mg/kg IV q8–12h		Severe renal or hepatic failure
Metoclopramide	Dopamine antagonist	0.2–0.4 mg/kg IM, IV *or* 1–2 mg/kg/24h IV CRI	CNS signs, interference with dopamine, constipation	GI obstruction, seizures
Misoprostol	Prostaglandin analogue	1–5 μg/kg PO q6–12h	GI upset, uterine contraction	Pregnancy, hypertension? seizures?

Abbreviations: CNS = central nervous system; CRI = constant rate infusion; ECF = extracellular fluid; GFR = glomerular filtration rate; GI = gastrointestinal; IM = intramuscular; IV = intravenous; RBF = renal blood flow.

nor these selective dopaminergic compounds have been evaluated in clinically affected ARF patients.

Osmotic diuretics are alternative agents for enhancing urine flow. Osmotic agents such as mannitol enhance urine production by increasing both intravascular volume and tubular fluid flow. Mannitol is freely filtered at the glomerulus and poorly reabsorbed in renal tubules, creating an osmotic effect such that water is not reabsorbed from the tubular lumen. Osmotic agents also prevent tubular and vascular obstruction by minimizing cellular swelling. Mannitol also possesses weak renal vasodilatory and cellular free radical scavenging actions (Burnier and Schrier, 1986). Adverse effects of mannitol infusion include volume overload and pulmonary edema, gastrointestinal upset, and central nervous system effects (usually at high doses). The drug is contraindicated for overhydrated or dehydrated patients and for patients with pre-existing cardiac disease or suspected intracranial hemorrhage. Some clinicians avoid giving mannitol to anuric patients.

Mannitol may be administered at a dosage of 0.5 to 1.0 g/kg IV as a slow bolus (over 15 to 20 minutes) (Kirby, 1989). Another protocol entails administration of partial dosages (0.5 mg/kg each) every 15 minutes for three treatments (Ross, 1989). Urine output should improve within 1 hour. A second bolus may be attempted if the agent is unsuccessful, but the potential for volume overexpansion and edema formation increases. When mannitol is beneficial, intermittent bolus injections (0.5 to 1.0 g/kg IV every 6 to 8 hours) or constant infusion of a 5% to 10% solution (2 to 5 mL/min) may be given up to 2 g/kg per day (Chew, 2000). One author recommends maintaining diuresis with an infusion of mannitol diluted in lactated Ringer's solution (Chew, 1992).

Hypertonic dextrose solutions have been useful as an alternative osmotic agent. Once the renal threshold for glucose transport has been exceeded, dextrose solutions create effects similar to those of mannitol on tubular flow and urine output. Solutions of 10% or 20% dextrose are formulated and administered as intermittent slow boluses of 25 to 50 mL/kg (over 1 to 2 hours) two or three times per day. The initial infusion rate may be as high as 2 to 10 mL/min in order to rapidly create hyperglycemia. The infusion rate may subsequently be dropped to 1 to 5 mL/min (Ross, 1989; Finco and Low, 1980). Advantages of dextrose solutions include low cost, availability, and relative safety. Dextrose solutions also provide nominal caloric supplementation. Urine glucose is easily monitored for assurance that sufficient hyperglycemia and filtration of glucose are continuing; urine volume still must be quantitated because glycosuria can occur without significant increases in urine production. Dextrose solutions may be inferior to mannitol in other respects, though, because the osmotic effects on cellular swelling and tubular obstruction will be minimized by intracellular equilibration of glucose across cell membranes, an effect that does not occur with mannitol (Chew, 1992). Hypertonic glucose also lacks the vasodilatory and free radical scavenging effects of mannitol. The rapid movement of glucose intracellularly does, however, minimize the potential development of vascular overload and pulmonary edema.

The choice of initial treatment protocol for oliguria varies with clinician preference, experience, available technical support, and patient variables. Furosemide and dopamine often are chosen initially because of their relative safety. Mannitol is probably, however, the preferred agent for treatment of nephrotoxic and ischemic renal failure in nonoverhydrated patients. If one protocol is ineffective, another protocol may be attempted. The effects of all measures to reverse oliguria appear to diminish as the duration of oliguria is prolonged.

Management of Hyperkalemia and Metabolic Acidosis

Patients with acute renal failure may be hypokalemic, normokalemic, or hyperkalemic. Hyperkalemia is most likely observed with oliguric or anuric renal failure. Management of hyperkalemia and other electrolyte disturbances is ideally based on serum electrolyte determinations; however, an estimate of potassium status can often be made on the basis of an electrocardiogram. Administration of potassium-free fluids and initiation of a diuresis is usually sufficient to correct mild to moderate hyperkalemia. Peaked T waves, bradycardia, prolonged PR intervals, flattened P waves, and widened QRS complexes may be seen with moderate elevations in serum potassium. Severe hyperkalemia may result in a loss of P waves, idioventricular rhythms, atrial standstill, or ventricular fibrillation and represents a life-threatening emergency. With severe electrocardiographic changes, administration of calcium gluconate (0.5 to 1.0 mL/kg of a 10% solution given IV over 10 to 15 minutes) offers cardioprotective actions. Calcium ions counteract potassium without lowering serum potassium; other measures must be initiated to prevent subsequent cardiac toxicity (Willard, 1987).

Bicarbonate administration facilitates an intracellular shift of potassium ions and is another useful initial treatment for moderate hyperkalemia. Sodium bicarbonate is administered as a slow intravenous injection of 0.5 to 2 mEq/kg (Willard, 1987). Alternatively, bicarbonate deficits can be determined based on serum bicarbonate, total CO_2, or base deficit measurement. The deficit is calculated by the formula: 0.3 × body weight (kg) × base deficit *or* (20 − serum bicarbonate or total CO_2 concentration). A portion of the deficit (usually one-fourth or one-half) is given as a slow bolus or in fluids, and the acid-base status is reassessed. An advantage of sodium bicarbonate administration is concurrent correction of co-existing metabolic acidosis. In the absence of hyperkalemia, bicarbonate administration is reserved for severe acidosis (blood pH <7.2 or total CO_2 <12 to 15 mEq/L). Overzealous bicarbonate administration may have serious detrimental results, including hypernatremia, hyperosmolality, ionized calcium deficits, reduced plasma potassium concentrations, metabolic alkalosis, and paradoxical acidosis of the cerebrospinal fluid.

An alternative method of therapy for acute hyperkalemia includes the administration of glucose (dextrose 0.1 to 0.5 g/kg as a 20% solution *or* 1 to 2 mL/kg 50% dextrose diluted to 25%) (Kirby, 1989). Administration of glucose triggers endogenous insulin secretion; both glucose and insulin facilitate intracellular movement of potassium. Protocols utilizing insulin and glucose (0.25 to 0.5 U/kg insulin followed by 1 to 2 g glucose per unit of insulin administered) have also been recommended. Exogenous insulin administration can promote hypoglycemia; blood glucose monitoring is required.

Disorders of calcium are occasionally found in acute renal failure. Hypercalcemia may be a cause of acute renal damage. Calcium levels usually drop with fluid or diuretic administration; investigation into the etiology of hypercalcemia should proceed, however. Severe hypocalcemia is rare except in ethylene glycol intoxication. Alkalinizing therapy may further reduce ionized calcium levels, resulting in symptomatic hypocalcemia. Calcium administration may be necessary in some cases.

Maintenance Fluid Therapy

Once a diuresis has been established, and in cases of nonoliguric acute renal failure, fluid therapy should be tailored to match urine volume and other sensible and insensible losses. Insensible losses (e.g., water lost from respiration) are estimated at 13 to 22 mL/kg per day. Urine output (the most variable sensible loss in patients with renal failure) is quantitated during 6- or 8-hour intervals; the amount lost is replaced during an equivalent period. Ongoing gastrointestinal losses also are estimated and replaced. Some clinicians factor in a 3% to 5% estimate to provide for subclinical dehydration each day, regardless of physical examination findings (except for signs of overhydration). Intervals can be extended as the animal is stabilized.

Fluid composition during maintenance therapy should be tailored to the individual. Polyionic replacement solutions that provide buffering activity and electrolyte replacement (e.g., lactated Ringer's solution, Normosol-R, Plasma-Lyte 56) may be administered during the first few days of treatment, especially if gastrointestinal or electrolyte losses are great. For longer term therapy, lower sodium solutions designed to meet maintenance fluid needs (e.g., half-strength lactated Ringer's solution or 0.45% saline in 2.5% dextrose, Normosol-M, or Plasma-Lyte 56) are preferred, as most ongoing losses will consist of free water losses in polyuria (Chew, 1992). Alternating administration of 5% dextrose solutions with high-sodium replacement solutions may also be effective in preventing hypernatremia in patients requiring long-term fluid therapy (Ross, 1989). Potassium supplementation in excess of amounts supplied in commercial fluids is usually required during the maintenance phase of treatment; a total of 20 to 30 mEq KCl per liter of fluid administered is typically sufficient.

Patient Monitoring Flowsheet: Chronic Renal Failure

Date					
Patient History*:					
Current medications					
Current diet					
Caloric intake					
Appetite					
Physical Examination*:					
Body weight					
Body condition					
Hydration status					
Blood pressure					
Fundic examination					
Clinical Pathology:					
Packed cell volume*					
Plasma protein*					
Serum albumin					
BUN/Urea*					
Creatinine*					
Phosphorus					
Calcium					
Sodium					
Potassium					
TCO_2 or HCO_3					
Urine-specific gravity					
Urine pH					
Urine protein					
Sediment					
Comments:					

Figure 29–1. Example of a flowsheet for monitoring the clinical and clinicopathologic features of chronic renal failure. *Minimal components of frequent serial monitoring.

21% of gross energy as protein (Polzin and Osborne, 1995). Products that provide high-quality protein in homemade diets include eggs, liver, cottage cheese, and lean meats.

Further reduction in protein intake should be reserved for refractory patients in which signs of uremia persist on the above diet. Excessive protein restriction may lead to protein malnutrition, hypoalbuminemia, and anemia. Protein or other nutrient deficiencies can inadvertently develop if adequate quantities of a moderately restricted diet are not consumed; intake of adequate energy should take precedence in dietary formulations. Protein depletion also may adversely affect renal function by contributing to alterations in renal hemodynamics and accentuating muscle catabolism, anemia, and acidosis. Animals with protein malnutrition exhibit weight loss, poor hair coats, and muscle wasting. Although reduced protein intake may improve clinical signs of renal disease, this dietary maneuver is unlikely to prevent renal disease in normal animals, dramatically slow progression of renal disease, or enhance renal function. Thus, the role of reduced protein intake in animals with early renal disease is less clear. Again, moderate restriction of protein may be appropriate in these individuals, with regular monitoring for evidence of protein malnutrition and for progression of azotemia.

Phosphorus

Restriction of dietary phosphorus is advocated for patients with renal failure to minimize hyperphosphatemia, secondary hyperparathyroidism, and dystrophic mineralization. Feeding to maintain a calcium × phosphorus solubility product below 60 to 70 is recommended to minimize soft tissue and renal mineralization. In experimental studies in dogs with induced renal disease, phosphorus and calcium restriction improved survival times but did not prevent renal mineralization (Brown et al., 1991).

Most reduced protein diets formulated for renal disease are also restricted in phosphorus content because meat proteins are the primary source of phosphorus in the diet. Appropriate canine diets are 0.13% to 0.28% phosphorus on a dry weight basis, providing 0.3 to 0.5 mg phosphorus/kcal, whereas feline diets are approximately 0.5% phosphorus, providing 0.9 mg phosphorus/kcal (Polzin and Armstrong, 1995). Supplemental phosphate-binding agents may be required if dietary restriction is inadequate to minimize hyperphosphatemia and normalize the calcium × phosphorus solubility product (see later discussions of dietary supplements and secondary hyperparathyroidism).

Sodium

Moderate sodium restriction is beneficial for dogs with renal disease, particularly those with systemic hypertension. Although single nephron adaptive responses are remarkably efficient for maintaining solute and water balance in renal disease, handling of large fluid and solute loads is limited, and conservation of water and solute is impaired. Sodium excretion increases with declining GFRs to maintain homeostasis; however, response to a sodium challenge may be impaired and excess sodium intake could lead to volume expansion. Conversely, sodium cannot be maximally conserved in the presence of acute restriction in intake or volume depletion. Diets should provide 15 to 50 mg/kg per day, usually 0.1% to 0.3% on a dry matter basis (Cowgill and Kallett, 1986). Changes in sodium intake should be made gradually if possible to avoid rapid changes in fluid homeostasis and extracellular fluid volume.

Lipids

Abnormalities of lipid metabolism in renal disease may lead to hypercholesterolemia, hypertriglyceridemia, and elevated low-density lipoprotein concentrations. High saturated fatty acid intake has been shown to accelerate glomerulosclerosis and progressive renal injury in rat models. Dietary lipid composition may be manipulated to minimize hyperlipidemia and protect renal function. Supplementation of omega-3 polyunsaturated fatty acids may be expected to favor vasodilatory eicosanoid production, inhibit intrarenal platelet aggregation, and minimize systemic and glomerular hypertension. Whether any appreciable effect of dietary lipid manipulation will be seen over the long-term course of chronic renal failure remains unknown (Brown, 1995; Bauer, 1995).

Energy

Appropriate caloric intake is a frequently overlooked goal of dietary management of renal failure patients. A catabolic state may be perpetuated despite the best manipulations of dietary content if sufficient calories for body energy requirements are not ingested. Energy depletion and protein malnutrition in turn exacerbate azotemia and hamper renal compensatory or regenerative responses. Energy requirements for patients with chronic renal failure have been estimated at 60 to 110 kcal/kg per day; a reasonable starting point is 75 kcal/kg per day (Brown, 1994). Frequent monitoring of body weight and body condition is imperative to ensure that appropriate weight is maintained.

As renal failure progresses, intake of appropriate calories becomes more important than the composition of the diet. Caloric supplements composed of fat and carbohydrate sources may be offered to provide additional energy. Occasionally, obese patients with renal disease are encountered. As obesity may contribute to systemic hypertension and impair other organ system functions, weight reduction is desirable in these patients. Adjustments in weight must be gradual, however, and excessive restriction of calories and protein intake should be avoided.

Dietary Supplements

Phosphorus Binders

If dietary phosphorus is ineffective in maintaining a serum phosphorus level of less than 6 mg/dL and a calcium × phosphorus solubility product less than 70, phosphorous-binding agents may be administered (Chew et al., 1992b). These agents are generally ineffective if dietary phosphorus is not restricted concurrently and must be given just before or with a meal. Liquid or encapsulated preparations are preferable to tablet forms, as they more readily mix with ingesta in the intestinal tract. Tablet forms can be crushed and given with food. Aluminum-based products (aluminum hydroxide, aluminum carbonate) are widely available and are administered at daily dosages of 30 to 90 mg/kg divided into two or three feedings (Polzin and Osborne, 1995). Magnesium-based products should be avoided in patients with renal failure (Chew et al., 1992b).

Calcium-based products (calcium acetate, 60 to 90 mg/kg per day; calcium carbonate, 90 to 150 mg/kg per day) are alternative phosphorus-binding agents with additional alkalinizing effects. Calcium-based products can also be used to minimize or correct hypocalcemia. Calcium acetate is recommended in normocalcemic to mildly hypercalcemic patients, as calcium carbonate is more likely to lead to hypercalcemia. Calcium-based products and aluminum-based agents also may be administered concurrently for added phosphorus-binding effects (Polzin and Osborne, 1995; Chew et al., 1992b). Serum calcium and phosphorus concentrations should be monitored every 2 weeks initially, then monthly or as needed during chronic therapy. Adverse effects of phosphorus-binding agents include nausea, gastrointestinal upset, constipation, and hypophosphatemia. Toxic effects of aluminum are theoretically possible with long-term administration, including anemia, encephalopathy, and osteomalacia (LLach and Bover, 1996).

Alkalinizers

Although dietary protein restriction helps reduce acid metabolites and metabolic acidosis, alkalinization therapy may be required in animals with moderate to severe metabolic acidosis. Chronic untreated metabolic acidosis may accelerate protein catabolism and azotemia, promote renal ammoniagenesis contributing to progressive renal tissue damage, and lead to increased calcium and potassium losses. Acid-base derangements also likely contribute to the clinical manifestations of renal failure, including anorexia, vomiting, and weight loss (Polzin et al., 1995; Giovanetti et al., 1992). Alkalinizing therapy is ideally planned based on serial blood gas analyses. Serum total CO_2 Tco_2 measurement is a reasonable guide to management in most patients. Oral alkalinization is recommended when bicarbonate or Tco_2 measurements fall below 15 to 17 mmol/L, whereas parenteral supplementation may be needed if the Tco_2 falls below 10 to 12 mmol/L.

Oral sodium bicarbonate may be administered at 8 to 12 mg/kg every 8 to 12 hours (1 mEq/cat every 8 to 12 hours for cats). Household baking soda supplies approximately 4000 mg bicarbonate/teaspoon (or 12 mEq bicarbonate/g); tablet preparations are also available. Alternatively, a 1 mEq/mL solution of bicarbonate can be prepared by adding 5 or 6 tablespoons of baking soda to 1 L of water (or one third of an 8 ounce box is added to 1 quart of water) (Polzin et al., 1995). Because of the added sodium intake, sodium bicarbonate may be inadvisable in hypertensive patients, and some clinicians prefer to use alternative alkalinizing agents in all renal failure patients. It is questionable, however, whether the sodium salt in sodium bicarbonate contributes to hypertensive disease in dogs and cats.

Alternative alkalinizing agents include potassium citrate (35 mg/kg orally [PO] every 8 hours or 0.3 to 0.5 mEq potassium/kg PO every 12 hours) and calcium carbonate or calcium acetate (100 mg/kg per day) (Brown, 1994; Lulich et al., 1992). These agents are particularly valuable when hypokalemia (potassium citrate), hyperphosphatemia, or hypocalcemia (calcium-based agents) is a concurrent problem (discussed elsewhere). Dosages of all alkalinizing agents may be titrated to effect. The goal of treatment is to modify bicarbonate concentrations to approximately 18 to 24 mmol/L. Overcorrection of acidosis can lead to metabolic alkalosis, hypokalemia, or ionized calcium deficits.

Potassium

Renal failure and metabolic acidosis have been identified as risk factors for hypokalemic myopathy in cats (Dow et al., 1987b; Dow and Fettman, 1992). Increased fractional excretion of potassium is observed, although 24-hour potassium loss is variable. Hypokalemia may be exacerbated by chronic metabolic acidosis, especially in cats fed acidifying diets. Potassium depletion in turn induces acidosis and depresses GFR, intensifying renal disease and potassium loss (Dow and Fettman, 1992; Dow et al., 1990; DiBartola et al., 1993). Supplementation of potassium to cats with renal insufficiency may stabilize or improve renal function. Most commercial renal diets have been adjusted to provide potassium beyond requirements for healthy animals, but cats with mild to moderate hypokalemia (K 3.5 to 4.5 mEq/L) will benefit from potassium supplementation at 2 to 5 mEq/day. Low-dose supplementation (2 mEq/cat per day) may be justified in normokalemic cats to prevent potassium depletion (Dow and Fettman, 1992). Cats with severe hypokalemia may require intensive replacement with intravenous potassium chloride or increased supplementation (5–10 mEq/day). Dogs with polyuric renal failure also may become hypokalemic. Potassium supplementation may be initiated at 1 to 6 mEq/kg per day if other dietary measures do not correct the hypokalemia (Brown, 1994). Potassium concentration should be carefully monitored in cats and dogs undergoing fluid diuresis for renal disease.

Potassium supplements are available in powder or liquid form for long-term oral administration. Potassium gluconate powder appears to be the most palatable and best tolerated product; flavored potassium gluconate elixirs also are available. Potassium citrate solution or diluted potassium chloride for injection (dilute 1:1 with water) also may be given orally. Gastrointestinal ulceration, nausea, vomiting, and food aversion may develop with liquid preparations.

Summary of Dietary Recommendations

Based on current information, the ideal diet for small animals in chronic renal failure should be moderately reduced in protein, phosphorous, and sodium content, contain high-quality protein sources, be highly digestible, and provide adequate potassium, nutrient, and caloric density. In a recent study, finding a diet appropriately modified in protein, phosphorus, lipids, and sodium was associated with stable renal function and delayed onset of uremia in dogs with CRF (Jacob, 2000a and 2000b). The composition and nutrient profiles for commercial "renal diets" are available from manufacturers' product information and summarized in a review by Bartges and Brown (2000). Dietary supplements or homemade diets may be required to meet the needs of individual patients.

Management of Anorexia and Vomiting

The best of dietary strategies is ineffective if the patient becomes anorectic, cannot consume adequate calories for energy needs, or is vomiting and intolerant of enteral feeding. Many metabolic consequences of renal failure may affect appetite, including hydration status, severity of uremia, degree of anemia, acidosis, secondary hyperparathyroidism, gastrointestinal complications, and electrolyte imbalances. In the sick, uremic animal, correction of dehydration, acidosis, electrolyte abnormalities, and gastrointestinal complications should be accomplished before attempts at introducing a "kidney diet" (Osborne et al., 1995). Supplementation of water-soluble vitamins and correction of anemia also may improve appetite. Angiotensin-converting enzyme inhibitors, some antimicrobials, and many other therapeutic agents can contribute to anorexia, and their potential benefit should be reviewed critically in intolerant patients.

In anorectic patients with chronic renal failure, a review of previous diets, dietary habits, and drug therapy is advised. As with all dietary changes, new diets should be introduced gradually, and small, more frequent meals may be preferable for many patients. Owners and nursing staff can tailor the feeding schedule and feeding environment to enhance appetite by avoiding hurried, noisy feeding or feeding in close association with painful or stressful procedures. Some animals respond to hand feeding or feeding during petting and socialization, especially in a quiet ward or outside the hospital area. Warming of food, moistening food, and ensuring easy access to food are practical methods of improving acceptance (Osborne et al., 1995). Flavoring agents can also be added, including animal fat, bullion, clam juice, tuna broth, brewer's yeast, garlic, butter, or cottage cheese (Polzin and Osborne, 1995; Osborne et al., 1991). An added benefit of flavored liquids is enhanced fluid intake, although broths high in sodium and phosphorus should be avoided. Supplementation of vegetable oils, margarine, cream, or complex sugars may be used to increase caloric intake (Brown, 1994). If oral ulcers that limit food intake are observed, application of xylocaine gels or cool tea flushes may be used to alleviate pain.

Gastrointestinal effects of uremia include mucosal irritation from nitrogenous waste products, impaired gastrointestinal mucosal barriers, and hypergastrinemia. Central receptors for appetite and nausea also are affected by retained substances and increased parathyroid hormone (PTH) concentrations. Anorexia, vomiting, and diarrhea are common complications of advanced renal failure. In patients with chronic renal failure, sporadic vomiting, nausea, and anorexia may be alleviated by the administration of histamine blockers such as cimetidine (5 mg/kg PO, intramuscularly [IM], or IV every 6 to 8 hours) or ranitidine (0.5 to 2.0 mg/kg PO every 12 hours). Cimetidine inhibits hepatic metabolism of many drugs, including β-blockers and calcium channel blockers, and should be avoided in patients receiving these drugs. The addition of sucralfate, a gastrointestinal mucosal protectant, may be useful for patients with severe gastritis or suspected gastrointestinal hemorrhage. Because sucralfate is most effective in an acidic stomach environment, other antiemetics or antacid medications should be given at least 30 minutes before the administration of sucralfate when used concurrently. For refractory vomiting, metoclopramide (0.2 to 0.4 mg/kg subcutaneously, IM, or PO every 8 hours) may be administered to improve gastric emptying and to reduce centrally mediated nausea.

Misoprostol, a synthetic prostaglandin analogue, inhibits gastric acid and pepsin secretion and has a cytoprotective effect on gastric mucosa. The drug may be useful in renal failure-induced gastritis at a dosage of 1 to 5 μg/kg PO every 6 to 8 hours. Transient gastrointestinal upset is a possible adverse effect of misoprostol administration that may be managed by adjusting the drug dosage and giving the drug with food (Plumb, 1995). Anorexia or gastrointestinal complications of drug administration must be addressed quickly in patients with renal failure, however, as dehydration and renal decompensation can occur.

Pharmacologic manipulation of appetite also has been attempted in anorectic patients. In the short term, intravenous administration of low-dose diazepam (0.05 to 0.15 mg/kg IV) may be successful in reviving appetite or stimulating food intake. Oral administration of benzodiazepines, such as oxazepam, may result in unacceptable sedation. Oral diazepam also has been associated with behavior changes and incidences of hepatic failure in cats. The metabolism of benzodiazepines may be reduced with concurrent administration of cimetidine. Other agents such as anabolic steroids, glucocorticoids, and progestins are of questionable benefit in stimulating appetite. Glucocorticoids should be avoided in most patients with renal failure because they may promote tissue catabolism, contribute to gastrointestinal ulceration, and result in fluid and sodium retention and glomerular hyperfiltration.

Management of Systemic Hypertension

Systemic hypertension is observed in more than 60% of dogs and cats with renal disease, particularly in animals with glomerular disorders, renal vascular disease, and renal neoplasia (Cowgill and Kallett, 1986). Multiple mechanisms may contribute to the development of hypertension in renal failure, including decreased glomerular filtration, impaired sodium and water handling, local activation of the renin-angiotensin-aldosterone system, and impaired production of renal vasodilatory substances. Clinical signs of hypertension in small animals are usually manifestations of ocular complications, including blindness, retinal hemorrhages, retinal detachment, and glaucoma, but they may include cardiac failure, neurologic signs, hemorrhage, and effusions. Overt signs are often inapparent, however, and blood pressure recordings should be routinely monitored in patients with renal disease.

Moderate restriction of sodium intake is the first step in management of mild systemic hypertension, along with weight reduction in obese animals. Dietary sodium content of 0.1% to 0.3% sodium by dry matter is recommended for initial management (Cowgill and Kallett, 1986; Littman, 1992). Most commercial to "renal" diets provide appropriate sodium content, limiting sodium intake to 10 to 40 mg/kg per day. Sodium restriction should be gradual in order to avoid precipitating volume depletion. If necessary, additional sodium restriction may be accomplished by feeding homemade diets or diets formulated for cardiac disease.

Pharmacologic manipulation of blood pressure may be indicated in animals with moderate to severe hypertension (systolic blood pressure >200 mm Hg), clinical signs attributable to hypertension, or persistent hypertension despite sodium restriction. The choice of agent must be based on the potential risks and benefits in the individual animal and the clinician's experience and preference. A variety of agents have been proposed for use in hypertension, including diuretics, beta β-blockers, ACE inhibitors, and calcium channel blockers. Diuretics are the mainstay of treatment of early volume-dependent hypertension in human patients; however, they may contribute to dehydration and potassium loss and may be inadvisable for patients with chronic renal failure. β-Blockers such as propranolol and atenolol are agents with negative inotropic and vasodilatory actions. Atenolol (2 mg/kg per day for cats, 0.25 to 2 mg/kg/day for dogs) may be preferred over propranolol because of its duration of action and β_1-receptor specificity. Atenolol is less likely to cause bronchoconstrictive side effects than propranolol (Littman, 1992). Both diuretics and β-blocking agents appear to be minimally effective in dogs with hypertension of renal failure, although β-blockers may be effective in cats (Ross, 1992). Clinical application now is limited.

Angiotensin-converting enzyme inhibitors and calcium channel blockers have received increased attention as antihypertensive agents for small animals because of their potential specific effects on renal microcirculation. Inhibition of angiotensin II production leads to decreased aldosterone secretion, decreased blood pressure, efferent arteriolar dilation, and reduced intraglomerular capillary pressure. Although these effects have not yet been proved to alter progression of renal disease, the agents may have value in minimizing glomerular hypertension (Brown, 1994). In glomerular disease, ACE inhibitors are helpful in controlling hypertension and minimizing proteinuria. Potential risks of ACE inhibitor administration include hypotension, decreased renal perfusion, hyperkalemia, gastrointestinal upset, and, rarely, myelosuppression or seizures. Excessive reductions in renal perfusion and GFR are most worrisome, as they may lead to acute decompensation of renal failure. To avoid this complication, administration of ACE inhibitors is initiated at a low dosage while blood pressure, blood urea nitrogen, and creatinine concentration are measured. The drug may be slowly increased to an effective dosage. Starting dosages of enalapril are 0.25 to 0.5 mg/kg PO per day.

Calcium channel blockers such as diltiazem or amlodipine also are attractive agents for the management of hypertension in patients with renal failure. Amlodipine (0.625 to 1.25 mg/cat/day PO) has become the preferred agent for cats (Henik, 1994). Calcium channel blockers reduce blood pressure by peripheral vasodilatory effects; potency varies with the preparation. Calcium channel blockers may preferentially dilate afferent renal arterioles, improving renal perfusion and glomerular filtration. They do not, however, reduce glomerular capillary pressure and do not attenuate development of glomerulosclerosis (Polzin and Osborne, 1995), although a nonhemodynamic inhibitory effect on glomerular hypertrophy may be observed (Ross, 1992). Calcium channel blockers also possess cytoprotective qualities that may be helpful in acute or chronic renal damage. Calcium channel blockers are negative inotropes and may cause hypotension, cardiac arrhythmias, and gastrointestinal upset in some patients.

Serial monitoring of blood pressure, hydration status, and renal and cardiac function is imperative for the appropriate management of hypertensive disease (reduction to approximately 150–170 mm Hg). Weekly blood pressure recordings should be made initially as dietary and then pharmacologic management is initiated. Biweekly or monthly recordings can be continued during maintenance treatment. Refractory hypertension may respond to combination therapy or addition of a direct vasodilator such as hydralazine. Administration of a calcium channel blocker with a β-blocking agent is avoided because of additive negative inotropic effects. Control of hypertension in patients with renal failure may slow the progression of disease and minimize the ocular, cardiovascular, and neurologic complications that may develop with uncontrolled hypertension.

Management of Secondary Hyperparathyroidism

Hyperphosphatemia, hypocalcemia, and impaired activation of vitamin D metabolites contribute to the development of secondary hyperparathyroidism in animals with renal failure. Parathyroid hormone plays an important role in regulating plasma calcium and phosphorous concentrations via effects on the gastrointestinal tract, kidney, and bone. The primary stimulus for PTH release is a drop in plasma calcium concentration; in renal failure phosphorous retention and hyperphosphatemia may lead to hypocalcemia. Additionally, and perhaps more importantly, impaired conversion of 25-hydroxycholecalciferol (25-hydroxyvitamin D) to the active 1,25-hydroxycholecalciferol (1,25-hydroxyvitamin D, or calcitriol) by 1-α-hydroxylase impairs gastrointestinal absorption of calcium. Calcitriol also plays an important role in the regulation of PTH by exerting an inhibitory (negative feedback) effect on PTH production and release.

The classic effect of secondary hyperparathyroidism in animals with renal failure is the development of renal osteodystrophy, usually seen as "rubber jaw," which results from excessive calcium and phosphorous removal from bone. This complication appears to be rare in dogs and cats but may develop with long-standing disease or in juvenile renal disease. Secondary hyperparathyroidism has, however, been implicated as a contributor to many other manifestations of uremia in human patients, including anemia, glucose intolerance, hyperlipidemia, encephalopathies, neuropathies, cardiac damage, muscle damage, and immunologic dysfunction. Furthermore, soft tissue mineralization associated with hyperparathyroidism may contribute to the progression of renal failure.

Dietary restriction of phosphorus, administration of phosphorus-binding agents, and calcium supplementation may be sufficient to minimize secondary hyperparathyroidism in early chronic renal failure (see earlier discussions of phosphorus binders and alkalinizers). Supplementation of the active vitamin D metabolite calcitriol may be valuable in further management of hyperparathyroidism and renal failure. Calcitriol acts to enhance calcium absorption in the intestines, enhance reabsorption of calcium in the kidneys, facilitate PTH-mediated removal of calcium from bone, and directly inhibit PTH secretion (Chew et al., 1993; Brown and Finco, 1995). Calcitriol supplementation should help normalize plasma calcium and phosphorous concentrations and minimize the clinical and clinicopathologic effects of secondary hyperparathyroidism.

Calcitriol supplementation has been recommended in low-dose (2.5 to 3.5 ng/kg per day) (Chew et al., 1993) and high-dose (6.6 ng/kg per day) (Brown and Finco, 1995) protocols. Formulations of 250- and 500-ng capsules are available; other doses may be prepared by special order.* Serum calcium concentrations should be normal and serum phosphorus concentrations should be maintained at less than 6 mg/dL before initiation of calcitriol supplementation. Frequent monitoring of calcium and phosphorus concentrations is required during administration. The first assessment should be completed 7 to 14 days after initiation of treatment, followed by monthly rechecks. Ideally, efficacy of treatment should be assessed by PTH measurements on pooled blood samples obtained before and during the first 6 months of treatment. The major complication of calcitriol supplementation is the development of hypercalcemia. Hypercalcemia can be managed by adjusting calcium-based phosphorus-binding agents used concurrently, reducing the dosage of calcitriol, or discontinuing administration of calcitriol temporarily and reinstituting the drug at a lower dosage when calcium concentrations return to normal (Chew et al., 1993). If phosphorus-binding agents are required to help normalize serum phosphorus, calcium acetate or aluminum-based binding agents may be preferable to calcium carbonate in order to minimize the propensity for hypercalcemia.

Calcitriol administration reportedly results in rapid reduction of serum PTH levels, normalization of serum calcium concentrations, and subjective improvement in the general well-being of treated dogs (Chew et al., 1993). Some investigators advocate its use early in renal failure as a method of improving quality of life in patients with renal failure and as a method of potentially slowing progression of renal disease. These effects are not well documented, however, and other investigators reserve calcitriol supplementation for animals in which documented hyperparathyroidism and progressive renal disease exist (Brown and Finco, 1995). As with other medical manipulations in patients with renal failure, careful monitoring of treatment is essential, with the potential benefits and possible risks weighed for each individual patient.

Management of Anemia

Progressive, nonregenerative anemia is a common complication of chronic renal dysfunction. Moderate to severe anemia is responsible for many of the clinical signs of renal disease, including apathy, lethargy, weakness, poor appetite, and poor body condition. A number of pathophysiologic mechanisms probably contribute to the anemia observed in renal failure, including depressed erythrocyte production, shortened red blood cell life spans, and blood loss due to gastrointestinal bleeding (King et al., 1992). Erythropoietin lack appears to be the most important mechanism of anemia. Dramatic responses to erythropoietin supplementation are seen in some cases.

Recombinant human erythropoietin (rhEPO), a genetically engineered replica of human erythropoietin, became available in the late 1980s and has been utilized for dogs and cats with anemia of renal failure. Erythropoietin is administered at an initial dosage of 100 U/kg subcutaneously three times weekly until the hematocrit is normalized. Target hematocrits are 0.37 to 0.45 L/L in dogs and 0.30 to 0.40 L/L in cats. Initial monitoring includes re-evaluation of packed cell volume or hematocrit measurements at 7- to 14-day intervals. In most cases rapid, progressive increases in red blood cell count, hemoglobin concentration, and hematocrit are observed, along with improvement in clinical parameters such as appetite, body condition, alertness, and activity (Cowgill, 1995a; Cowgill et al., 1990). Lower initial dosages (50 to 75 U/kg) may be used if a slower response is desired or if the drug is cost prohibitive. If a response is not observed in 3 to 4 weeks, the dosage may be increased incrementally to 125 to 150 U/kg three times weekly. As target hematocrits are reached, the dosage and frequency of administration are tapered, with required maintenance dosages usually at 75 to 100 U/kg every 4 to 7 days. Follow-up monitoring can then be performed at monthly intervals if a stable clinical course has been observed.

Unfortunately, resistance to rhEPO is observed in some dogs and cats after several weeks of treatment. Anti-rhEPO antibodies are formed in 25% to 50% (Cowgill, 1995a) of treated patients, blocking the erythropoietic effect. A rapid decline in hematocrit, red blood cell count, and hemoglobin concentration, along with erythroid hypoplasia of the bone marrow, is observed 4 to 16 weeks after initiation of therapy. Anti-rhEPO antibodies may also interfere with remaining endogenous erythropoietin and result in life-threatening anemia or a transfusion-dependent anemia. Because of the potential development of cross-reacting antibodies, rhEPO treatment is generally reserved for dogs and cats with symptomatic severe anemia, usually when the hematocrit drops below 20% to 25% in dogs or 17% to 20% in cats.

A suboptimal response to rhEPO treatment also may be attributed to depleted iron stores. Iron status, including serum iron concentration and total iron-binding capacity, should be evaluated before initiating treatment and re-evaluated monthly or if apparent resistance to treatment is observed. Some authors recommend iron supplementation for all animals treated with rhEPO (Cowgill, 1995a). Ferrous sulfate is given orally at a dosage of 100 to 300 mg/day (dogs) or 50 to 100 mg/day (cats). Systemic and intra-

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*Island Pharmacy Services, Inc., PO Box 23124, Hilton Head Island, SC 29925-3124 (1-800-328-7060).

useful in the early management of toxicoses, especially ethylene glycol intoxication. In chronic renal failure, dialysis is considered when uremic signs are unresponsive to therapy, usually when azotemia is advanced. The procedure requires reliable vascular access, an appropriate hemodialyzer and dialysis delivery system, and dedicated technical team (Cowgill and Maretzki, 1995; Langston et al., 1996). Currently hemodialysis is available at the University of California—Davis Companion Animal Dialysis Unit, Davis, California; the Veterinary Referral Specialty Practice, Gaithersburg, Maryland; and the Animal Medical Center, New York, New York. The development of additional centers for intermittent dialysis in dogs may increase the application of the technique for improved management and prolonged survival in selected cases.

Peritoneal dialysis may be initiated in the practice or referral center setting after placement of an intra-abdominal dialysis catheter. Straight, acute peritoneal dialysis catheters are available for emergency dialysis, whereas column disc or T-fluted catheters are preferred for long-term dialysis. Dialysate solutions of 1.5% to 4.25% dextrose are infused to create an osmotic gradient within the abdomen. Substances such as urea, creatinine, phosphorus, electrolytes, and other uremia molecules can pass through intercellular channels of the peritoneum into the dialysate for removal. A dedicated technical support team is required to manage the frequent exchanges and potential complications of the procedure. Peritonitis, hypoalbuminemia, electrolyte abnormalities, and leakage around the catheter are common complications (Lane et al., 1992).

RENAL TRANSPLANTATION

Renal transplantation is the definitive mode of management of chronic renal diseases in human patients and has become a viable option in veterinary medicine in selected circumstances. A successful clinical renal transplantation program has been developed for cats at the Veterinary Medical Teaching Hospital, University of California, Davis (Gregory et al., 1992; Gregory, 1993; Gregory and Gourley, 1993). With transplantation of a healthy donor kidney and appropriate immunosuppressive therapy, uncomplicated cases can expect good quality survival times of 1 to 3 years post-transplant. The best candidates for renal transplantation are cats in early renal failure, with less than 20% weight loss and no other disease conditions. Candidates are screened for cardiac disease, urinary tract infection, feline leukemia virus, and feline immunodeficiency virus.

Immunosuppressive therapy with cyclosporine and prednisolone is initiated perioperatively and continued indefinitely. Treatment is monitored by frequent measurements of trough blood levels of cyclosporine. Potential complications of transplantation include anesthetic and surgical complications, obstruction of the transplanted ureter, infections caused by excessive immunosuppression, pyelonephritis, and acute or chronic graft rejection. Transplantation cannot be regarded as a cure for renal disease or an option for emergency treatment of renal failure, but it can be expected to provide an improved quality of life and enhanced survival in some cats with renal failure. Details of the program, surgical procedure, and criteria for case selection are available (Gregory, 1993; Gregory and Gourley, 1993).

MANAGEMENT OF MICTURITION DISORDERS

Physiology of Micturition

The storage phase of micturition is characterized by sympathetic dominance, with sympathetic innervation to the bladder and urethra supplied by the hypogastric nerve. Activation of β-adrenergic receptors in the urinary bladder facilitates relaxation of the detrusor muscle, whereas stimulation of α-adrenergic receptors in the bladder neck and urethra facilitates smooth muscle contraction and closure of the outlet. Additional urethral resistance is supplied by the striated muscle of the external urethral sphincter. As bladder volume and pressure increase with filling, afferent information is transmitted to the central nervous system via the pelvic nerve and spinal afferent pathways. Voiding is initiated by voluntary control centers in the cerebral cortex and midbrain. Efferent impulses are transmitted via spinal pathways and the pelvic nerve in the parasympathetic system, initiating contraction by stimulating cholinergic receptors in the detrusor muscle of the urinary bladder. The sympathetic input to the bladder and urethra is inhibited, allowing outlet resistance to drop appropriately. After complete voiding, the system is reset for storage (deGroat and Booth, 1980).

Disorders of urine storage usually result in urine leakage, whereas disorders of voiding result in urine retention, incomplete voiding, or incontinence. Most disorders of micturition can be classified and managed based on the status of urinary bladder (hypocontractile or hypercontractile) and urethral (hypotonic or hypertonic) function (Moreau and Lappin, 1989; Barsanti, 1993). Diagnosis is usually based on evaluation of historical, physical, and observational findings, although specialized urodynamic testing is required in some instances. Pharmacologic agents are valuable in the management of functional micturition disorders; manipulation of urinary bladder or urethral smooth muscle tone can aid in facilitating normal micturition. Because pharmacologic activity is directed at the end organ (postganglionic receptors in the urinary bladder or urethra), agents are applied similarly in both neurogenic and non-neurogenic disorders (Table 29–3).

The Hypocontractile Urinary Bladder

Problems resulting in hypocontractile urinary bladders include sacral or suprasacral neurologic lesions, acute or chronic overdistension of the urinary bladder, disorders causing general muscle weakness, or dysautonomia. Urinary bladder contraction is primarily controlled by parasympathetic (cholinergic) input. Cholinergic agents have been used to promote bladder emptying in atonic bladders, although the success of orally administered agents is unreliable (Finkbeiner, 1985). Bethanechol chloride is administered at starting dosages of 1.25 to 2.5 mg (cats), 5 mg (small dogs), and 10 mg (larger dogs) every 8 to 12 hours. Full effects of the drug should be apparent within 1 to 2

search for underlying urinary tract infection, neurologic abnormalities, and other causes of incontinence is indicated.

The Hypertonic Urethra (Functional Urethral Obstruction)

Inappropriate urethral resistance may lead to functional urethral obstruction and urine retention. Urethral inflammation or spasm can develop after urethral obstruction with uroliths or urethral plugs. Urethral resistance also may be uncoordinated with bladder contraction as a result of neurologic disorders or idiopathic causes. Urethral resistance also may increase when bethanechol is administered for hypocontractile urinary bladders; the drug also stimulates contractions of musculature at the bladder neck. In these situations, pharmacologic manipulation may be instituted to decrease smooth or striated muscle contractility in the urethra and reduce outlet resistance.

α-Adrenergic Antagonists

α-Adrenergic antagonists are the preferred agents for decreasing urethral smooth muscle tone and are experimentally effective in reducing overall urethral resistance in dogs (Khanna and Gonick, 1975). Their activity is less predictable in cats, in which striated muscle predominates in the urethra. Phenoxybenzamine has been a commonly used α-antagonist in both dogs and cats (Barsanti et al., 1996; Lees, 1994). Phenoxybenzamine irreversibly inactivates α-receptors and may have a central effect on striated musculature (Wein, 1994). The drug is available in 10-mg capsules and is dosed at approximately 0.25 mg/kg PO every 12 to 24 hours (Moreau and Lappin, 1989). Total dosages usually range from 5 to 20 mg (dogs) and 2.5 to 5 mg (cats). Efficacy may be discerned by judging the quality of urine stream produced. Phenoxybenzamine is expensive, sometimes difficult to obtain, and is only available via an emergency drug release in Canada. The drug's availability may be further limited because of the discovery of its carcinogenic potential in rats (Wein, 1994).

An alternative, and more selective, α_1-antagonist is prazosin (Fischer et al., 1998), a drug that has been recommended in the management of heart failure and systemic hypertension in dogs. Extrapolated dosages are 1 mg per 15 kg body weight PO every 8 to 12 hours in dogs; dosages of 0.25 to 0.5 mg every 8 to 12 hours seem reasonable for cats. Because total dosages of 1.5 to 3 mg PO every 8 hours are used for functional urethral obstruction in humans, however, lower dosages may be effective in small animals. Additional α-blocking agents on the horizon include terazosin and doxazosin (Wein, 1994). No information is yet available regarding their use in small animals.

Adverse effects of α-antagonists include hypotension, reflex tachycardia, and gastrointestinal irritation. Nausea can be minimized by administration of the drug with food. The drug may be dangerous to animals with cardiac disease receiving other vasodilators or diuretics and to animals with renal disease, in which drops in perfusion pressure could precipitate an acute crisis. Any evidence of weakness should prompt withdrawal of the drug or adjustment of the dosage.

Striated Muscle Relaxants

If manipulation of urethral smooth muscle does not sufficiently improve voiding, addition of a striated muscle relaxant may be considered. Striated muscle relaxants are particularly useful in dysuric patients with upper motor neuron lesions and in cats with functional urethral obstruction. In this species striated muscle predominates in the distal urethra and likely contributes most to functional obstruction. The most common muscle relaxant used for urethral resistance is the benzodiazepine diazepam. The drug serves as a short-acting muscle relaxant by centrally mediated actions, and its effect on urethral striated muscle is variable.

Diazepam (0.2 to 0.5 mg/kg PO) is recommended as a temporary agent to facilitate bladder expression or to augment weak voiding; the agent is given 15 to 30 minutes before expression (Lees, 1994). Dosages for cats range from 1.25 to 2.5 mg/cat every 8 to 12 hours; sedation is common with higher dosages (Lees, 1994; Barsanti et al., 1996). In dogs, total dosages of 2 to 10 mg/dog are given (Labato, 1992; Rosin and Ross, 1981). Adverse effects of diazepam administration include sedation, weakness, and paradoxical excitement. In cats, behavior changes and idiosyncratic hepatotoxicity are additional concerns.

Dantrolene is an alternative striated muscle relaxant that has recently been investigated in cats. Dantrolene acts as a direct muscle relaxant by inhibiting calcium movement from the sarcoplasmic reticulum in muscle cells. The agent (1 mg/kg IV) was effective in reducing segmental urethral pressures in healthy male cats (Straeter-Knowlen et al., 1994) and in moderately reducing urethral pressures in a small group of recently obstructed cats (Straeter-Knowlen et al., 1995). The effect on urethral musculature was enhanced by the concurrent administration of prazosin (Straeter-Knowlen et al., 1995). Recommended oral dosages are 1 to 5 mg/kg PO every 8 hours in dogs and 0.5 to 2.0 mg/kg PO every 8 hours in cats (Polzin and Osborne, 1985). Potential adverse effects include sedation, dizziness, weakness, and gastrointestinal upset; the drug is contraindicated in patients with cardiopulmonary disease. Hepatotoxicity is a worrisome adverse effect of dantrolene administration in people, usually after long-term treatment at high dosages (Plumb, 1995). Clinical reports regarding the use of oral dantrolene in small animals are lacking.

Treatment of detrusor-urethral dys-synergia has been unrewarding in reported cases (Barsanti et al., 1996; Blackwell, 1993; Collins et al., 1986; Gookin and Bunch, 1996). In the author's experience, dogs with dysfunctional voiding in the absence of compressive neurologic disease are often responsive to manipulation of smooth muscle resistance. Pharmacologic manipulation of urethral tone in cats with dys-synergia or functional obstruction and dogs with suspected striated urethral dyssynergia is less rewarding. Recovery is also related to the degree of detrusor damage sustained by the time of diagnosis. Detrusor-urethral dyssynergia associated with acute, reversible neurologic disease usually has the best prognosis for recovery.

DRUGS USED IN THE MANAGEMENT OF FELINE LOWER URINARY TRACT DISEASE

Idiopathic hematuria, dysuria, and urethral obstruction is a common clinical problem encountered in cats. *Feline urologic syndrome, idiopathic feline lower urinary tract disease* (iFLUTD), *idiopathic feline hematuria*, and *feline interstitial cystitis* all are terms that have been used to describe this combination of clinical signs when urinary tract infection, urolithiasis, neoplasia, and other causes have been ruled out. Many pharmacologic agents and treatment strategies have been proposed for management of this disorder and for prevention of recurrence. The apparent efficacy of any therapy for cats with idiopathic disease should be considered in light of the usual self-limiting nature of this disorder, and pharmacologic agents should be administered only after assessment of the likely benefits and possible risks of each treatment (Kruger, 1996; Kalkstein et al., 1999).

Urinary Acidifiers

Manipulation of urine pH, usually by dietary means, has become a common strategy for management of FLUTD. The strategy is most likely to be helpful in cats in which struvite crystalluria is a significant component and does not eliminate recurrence in all cats with idiopathic disease (Kruger et al., 1996; Buffington and Chew, 1994). Supplemental acidifiers such as ammonium chloride and DL-methionine are considered if nonacidifying diets are consumed. Acidifying agents supply an acid load that results in consumption of bicarbonate buffer and acidification of body fluids. As the acid load is excreted to maintain homeostasis, acid urine is produced (Taton et al., 1984). The recommended dosages of ammonium chloride range from 40 to 200 mg/kg per day, whereas DL-methionine is administered at a dosage of 200 to 1500 mg/cat per day. The agent is given with food once or twice daily. Adverse effects include gastrointestinal upset and vomiting. A combination agent with reduced amounts of ammonium chloride and DL-methionine (UROEZE) has been recommended to minimize nausea associated with urine acidifiers (Senior et al., 1986).

Overacidification is another possible complication of urine acidification in cats; young cats and cats with renal insufficiency are most susceptible. Long-term administration of urinary acidifiers may contribute to metabolic acidosis, hypokalemia, bone and mineral imbalances, renal failure, and calcium oxalate urolithiasis (Ching et al., 1992; Dow et al., 1987a; Kirk et al., 1995). Heinz body anemia and methemoglobinemia have been observed in kittens treated with DL-methionine as well as in adult cats treated with high dosages (Maede et al., 1987). Arrhythmias and central nervous system depression are serious complications of high-dose ammonium chloride administration. Both agents are contraindicated in patients with hepatic disease, as the administration of an ammonium load may potentiate hepatoencephalopathy. Serial monitoring of clinical status, complete blood counts, acid-base, and electrolytes is recommended during therapy.

Urinary Antiseptics

Urinary antiseptic agents have been considered as adjunctive treatment in FLUTD because of their antiviral activity (Kruger et al., 1996). Viruses including herpesvirus, feline syncytia-forming virus, and feline calicivirus have been implicated in the etiopathogenesis of FLUTD, although a consistent cause and effect relationship has been difficult to establish. The agents are more commonly used for antibacterial and antifungal properties, but these are uncommon causes of urinary disease in cats. The most commonly suggested antiseptic for small animal usage is methenamine, a cyclic hydrocarbon administered in combination with either mandelic acid (methenamine mandelate) or hippuric acid (methenamine hippurate). Mandelic acid and hippuric acid serve to acidify the urine and may exhibit some additional antimicrobial activity. With sufficient contact time in acidic urine, methenamine is converted to formaldehyde, a potent antimicrobial agent. Methenamine is contraindicated for patients with renal or hepatic insufficiency, and its use may contribute to overacidification like other urinary acidifiers. Other antiseptics or analgesics containing methylene blue or azodyes should be avoided in cats because of the potential for development of Heinz body hemolytic anemia.

Glucocorticoids

Glucocorticoids have been recommended to alleviate urinary bladder or urethral inflammation in cats with iFLUTD. Anti-inflammatory effects of glucocorticoids on leukocyte migration, vascular permeability, and arachidonic acid metabolism would be expected to suppress the inflammatory symptomatology and hematuria associated with this disorder. Treatment is based on the assumption that persistent inflammation leads to hematuria. Although it appears that glucocorticoids do little to alter the course of typical idiopathic lower urinary tract disease (Osborne et al., 1996), some clinicians recommend glucocorticoid administration (prednisone or prednisolone 1.0 to 2.0 mg/kg every 24 hours) in cats exhibiting chronic, recurrent, or refractory idiopathic hematuria and dysuria (Ross, 1990). No convincing evidence has been presented to establish that glucocorticoids alter the natural course of iFLUTD, however.

Glucocorticoid administration also is not without risk. Refractory urinary tract infection and pyelonephritis may develop, especially when glucocorticoids are administered to cats with indwelling urinary catheters (Barsanti et al., 1992). Prophylactic antimicrobial treatment does not appear to reduce the risk of catheter-induced infection. Glucocorticoids must be considered contraindicated for cats with urinary catheters in place or with evidence of bacteriuria. The catabolic effects of glucocorticoids also may be hazardous in debilitated, azotemic, or dehydrated cats (Kruger et al., 1996).

Antispasmodic Agents

Agents that relax smooth or striated muscle of the urinary tract have been advocated for symptomatic relief of pollaki-

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Therapy of Cardiovascular Diseases 30

Dawn Merton Boothe

- CARDIOVASCULAR PHYSIOLOGY AS IT PERTAINS TO CARDIOVASCULAR DRUGS
  - Myocardial Contractility
  - Adrenergic Receptors
  - The Action Potential of Cardiac Muscle
  - Smooth Muscle of the Vasculature
  - The Role of Nitric Oxide
- PATHOPHYSIOLOGY OF CARDIAC DISEASE AS IT RELATES TO DRUG THERAPY: CONGESTIVE HEART FAILURE
- VASODILATOR THERAPY
  - Arterial Vasodilators
  - Hydralazine
  - Calcium Channel Blockers
    - Pharmacodynamic Effects
    - Clinical Pharmacology
    - Drug Interactions and Side Effects
    - Clinical Use
  - Angiotensin-Converting Enzyme Inhibitors
    - Pharmacodynamic Effects
    - Clinical Pharmacology
    - Clinical Use
  - Other Angiotensin-Converting Enzyme Inhibitors
  - Arterial and Venous Dilators
    - Organic Nitrates
    - Sodium Nitroprusside
    - Prazosin
    - Nitroglycerin
- ANTIARRHYTHMIC DRUGS
  - Cardiac Arrhythmias
  - Class I Antiarrhythmic Drugs
    - Quinidine
    - Procainamide
    - Disopyramide
    - Class IB Drugs
    - Class IC Drugs
  - Class II Antiarrhythmic Drugs
    - Nonselective β-Blockers
    - Selective β-Blockers
  - Class III Antiarrhythmic Drugs
  - Class IV Antiarrhythmic Drugs
    - Diltiazem
    - Verapamil
  - Miscellaneous Antiarrhythmic Drugs
- POSITIVE INOTROPES
  - Digitalis and Other Cardiac Glycosides
    - Structure-Activity Relationship and Mechanism of Action
    - Clinical Pharmacology
    - Preparations and Dosing Information
    - Drug Interactions
    - Clinical Efficacy
    - Toxicity and Side Effects
    - Clinical Use
  - Phosphodiesterase Inhibitors
    - Methylxanthine Derivatives
    - Bipyridines
  - β-Adrenergic Agonists
    - Dopamine
    - Dobutamine
    - Epinephrine
    - Isoproterenol
    - Miscellaneous Agents
- NEGATIVE INOTROPES
- TREATMENT OF SPECIFIC VASCULAR DISORDERS
  - Acquired Valvular Diseases
    - Chronic Mitral Valve Insufficiency
    - Tricuspid Valvular Insufficiency
  - Diseases of the Myocardium
    - Dilated Cardiomyopathy
    - Feline Dilated Cardiomyopathy
  - Hypertrophic Cardiomyopathy
    - Pathophysiology
    - Treatment
  - Systemic Hypertension
  - Cardiac Arrhythmias
    - Superventricular Arrhythmias
    - Ventricular Arrhythmias
  - Bradyarrhythmias
  - Pericardial Effusion
    - Pathophysiology
    - Pharmacologic Management
- HYPERTHERMIA
- SHOCK
  - Classification of Shock
    - Hypovolemic Shock
    - Cardiogenic Shock
    - Distributive Shock
  - Pathophysiology
    - Sequelae of Cellular Ischemia
    - Oxygen Free Radicals
    - Role of Nitric Oxide
    - Gastrointestinal Barrier
  - Treatment
    - Fluid Therapy
    - Blood and Blood Substitutes
    - Pressor Drugs
    - Miscellaneous Drugs
  - Cardiopulmonary Cerebrovascular Resuscitation
    - "Crash Cart" Drugs
    - Cardiopulmonary Cerebrovascular Resuscitation Conditions
- HEARTWORM DISEASE (DIROFILARIASIS)
  - Physiology and Pathophysiology
  - Occult Heartworm Disease
  - Therapy
    - Pretreatment Assessment
    - Severe Pulmonary Arterial Disease and Pretreatment Therapy
    - Pneumonitis
  - Adulticide Therapy
    - Adulticide Drug Options
    - Drug Therapy
    - Thiacetarsamide
    - Melarsomine Therapy
    - Alternative Adulticides
  - Microfilaricide Therapy
  - Prophylactic Therapy
  - Feline Heartworm Disease

CARDIOVASCULAR PHYSIOLOGY AS IT PERTAINS TO CARDIOVASCULAR DRUGS

Myocardial Contractility

The rationale for the use of inotropic agents is based on mechanisms of myocardial contraction. The inotropic state of the muscle reflects the relationship between resting fiber length and peak isometric tension. The myocardium develops force for contraction and thus the strength to pump blood by forming cross-bridges between actin and myosin myofilaments in cardiac muscle. The amount of force that the muscle can generate depends on the number of cross-bridges that form when myosin engages actin. Energy (adenosine triphosphate [ATP]) causes a sliding motion between the proteins of the myofilaments and cardiac muscle to shorten and develop force.

The interaction between proteins in the myofilament is regulated by troponin. Troponin is formed from three proteins. Calcium binds to one protein of troponin, forcing a conformational change in another protein, tropomyosin, which normally prevents the interaction between actin and myosin. When tropomyosin changes in conformation, it can no longer prevent the formation of cross-bridges between actin and myosin. The force that develops as actin and myosin interacts depends on the amount of calcium that binds to troponin, which, in turn, is regulated by the concentration of intracellular calcium.

There are multiple sources of intracellular myocardial calcium (Fig. 30–1). Extracellular calcium can enter the myocardial cell through "slow" electrogenic or voltage-gated calcium channels or through Na^+-Ca^{2+} exchange channels that utilize cell membrane ATPase (Adams, 1995b; Kelly and Smith, 1995). When depolarization occurs (i.e., an action potential), the rapid Na^+ flux in the cell is a signal to "turn on" the slow calcium channel, thus causing a rapid rise in intracellular calcium. This rapid influx of calcium into the cell stimulates the release of calcium from intracellular storage sites. The sarcoplasmic reticulum (a site of calcium sequestration) and mitochondria are intracellular storage sites. Of the two, the sarcoplasmic reticulum is more significant in quantity and possibly function. Relaxation of the myocardial muscle does not occur until the intracellular calcium concentration falls as it is resequestered into the sarcoplasmic reticulum and extruded outside of the cell. Both are energy (ATP)-requiring processes.

The velocity and extent of cardiac muscular contraction

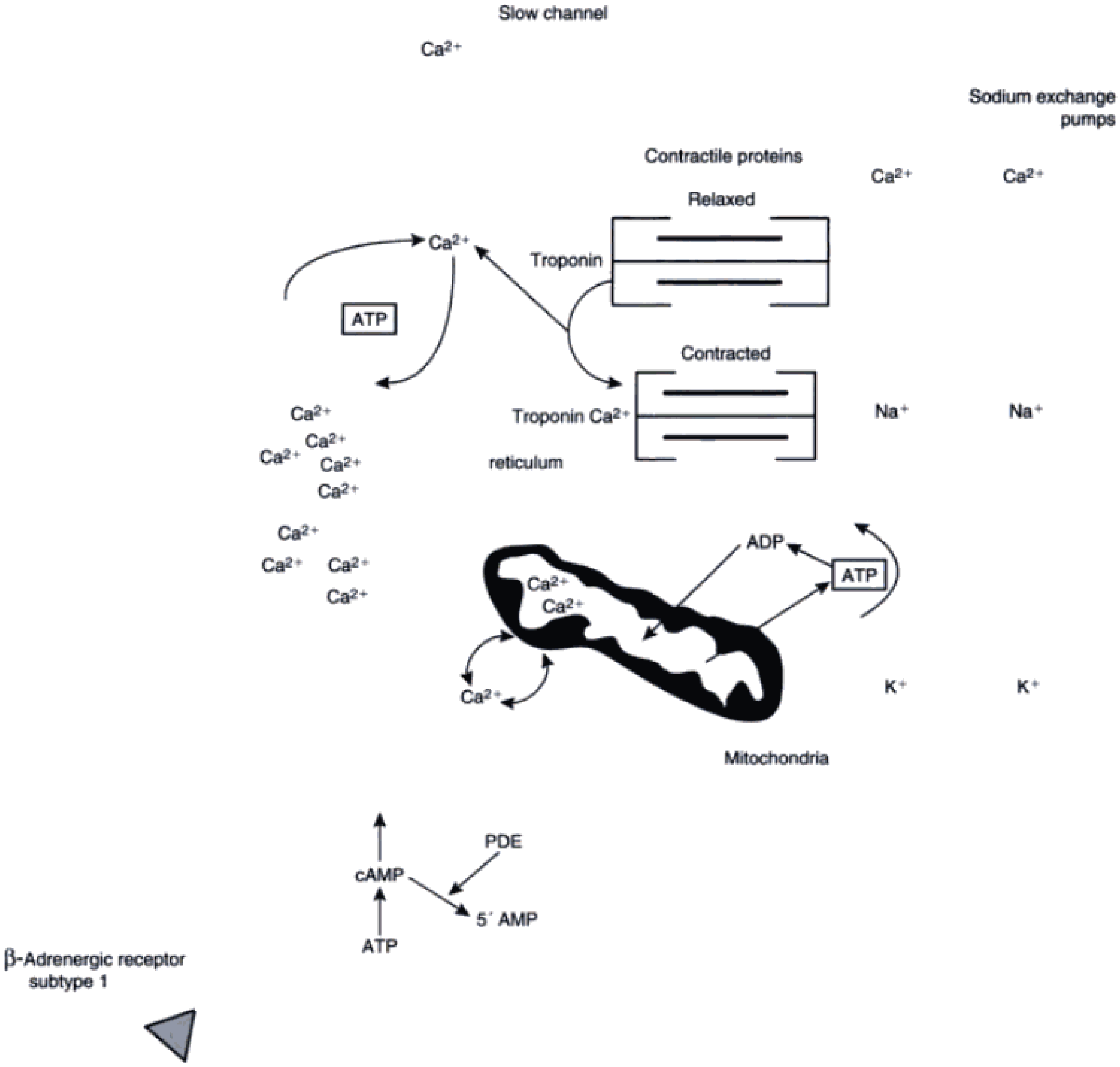

Figure 30–1. Calcium can enter the myocardial cell through several mechanisms, including the slow calcium channel (accompanies the action potential), the sodium/calcium exchange ATPase pump, and β_1-adrenergic receptor stimulation. Increased intracellular concentrations of calcium lead to the release of sarcolemmal calcium. Calcium leads to the interaction between actin and myosin, causing myocardial contractility. Sequestration of calcium in the sarcoplasmic reticulum causes myocardial relaxation. ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; PDE = phosphodiesterase.

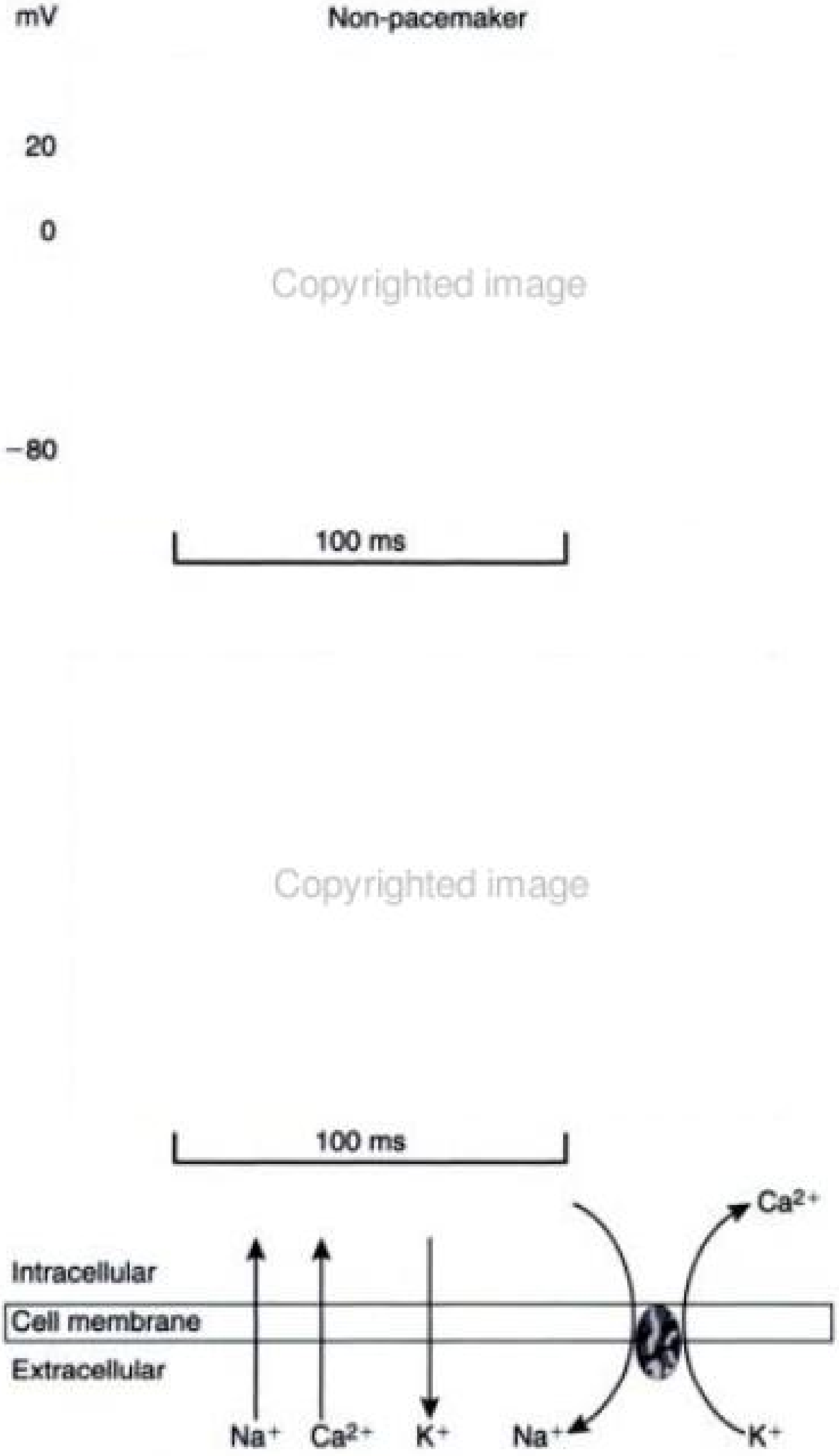

Figure 30–2. The action potential (AP) occurs in four phases. Phase 0 occurs when the resting membrane potential reaches threshold, resulting in the generation of the AP. The rapid upswing in the membrane potential reflects sodium and, to a lesser degree, calcium influx. In cells capable of automaticity (bottom), calcium is the primary ion moving inward during phase 0. This calcium influx stimulates release of calcium from the sarcoplasmic reticulum. Phase 1 represents the early phase of repolarization. An influx of chloride and decreased efflux of potassium lead to reestablishment of the membrane potential. During phase 2, electrogenic movement of calcium through "slow" channels prolongs repolarization, causing a plateau phase. With phase 4, the membrane potential reaches the diastolic resting level. In cells capable of automaticity, this phase is characterized by a gradual depolarization, probably due to calcium influx, until threshold is reached. The heart rate is determined by the slope of phase 4; tissues with the steepest phase 4 slope will serve as the cardiac pacemaker.

The specialized tissues of the heart differ from those of myocardium for at least two reasons. First, phase 0 depolarization largely depends on movement of Ca^{2+} through the slow channel. This renders these tissue more susceptible to the effects of calcium channel blockers (Robertson and Robertson, 1995). Second, phase 4 of the specialized tissues is characterized by a slow spontaneous discharge that continues to raise the membrane potential above the resting state until threshold for an action potential is reached. These tissues are capable of automaticity. The drift toward depolarization is probably due to the involvement of a slow calcium channel in phase 0. The rate at which the fibers "fire" or generate an impulse depends on the rapidity with which phase 4 reaches threshold, that is, the slope of phase 4. The sinoatrial node is the pacemaker tissue for heart rate because the tissues in this region have steeper phase 4 slopes. A steeper slope means less time taken to reach action potential threshold. Tissues with the steepest slope are capable of generating an impulse faster than other specialized fibers. Thresholds of the conducting tissues and the Purkinje fibers are less steep than the sinoatrial node but more steep than myocardial tissue. They can also serve as pacemakers in the event that the sinoatrial node does not generate an impulse. The slope of phase 4 can change in myocardial tissue that has been diseased, allowing these tissues to generate impulses at a rate faster than the sinoatrial node.

The cell is inexcitable or nonresponsive to additional stimuli during the early and intermediate phases of the action potential cycle and only partially responsive if stimulated before complete repolarization has occurred and the resting membrane potential has returned to normal. The terms *effective refractory period* and *absolute refractory period* are used to refer to the period of unresponsiveness. The refractory period limits the rate at which myocardial tissues can respond to impulses.

Conduction velocity is the speed of impulse propagation through cardiac fibers. It is determined by the rate at which depolarization occurs (phase 0) and the final "height" of the action potential. The velocity of conduction is directly proportional to the rate and magnitude of phase 0 depolarization (and therefore Na^+ influx). The faster depolarization (phase 0) occurs and the greater the magnitude, the stronger the ability of the impulse to depolarize surrounding cardiac fibers. The interrelationship between phase 4 and phase 0 is important because it is this relationship that determines the conduction velocity of cardiac impulses.

Smooth Muscle of the Vasculature

Myocardial oxygen demand is directly related to heart rate, myocardial wall tension, and the inotropic state of the myocardium (Adams, 1995b). Myocardial wall tension is determined by the size of the ventricle and the intraventricular pressure. Thus, tension is impacted by preload (end-diastolic volume and stretch) and afterload (aortic blood pressure). Drugs that decrease systemic arterial pressure (e.g., drugs that dilate arterioles) will decrease left ventricular afterload. More blood will be ejected into systemic circulation, diverting blood from the pulmonary vasculature. Left ventricular filling (preload) and thus wall size and tension will decrease, as will myocardial oxygen demands. Reduction of either preload or afterload can reduce cardiac work without impacting inotropic effects on the myocardial muscle.

The excitation-contraction coupling mechanism in vascular smooth muscle depends on calcium influx. Calcium can enter the vascular cell via either voltage-sensitive (electrogenic) signals that occur with depolarization or, more commonly, through receptor-operated Ca^{2+} channels. Intracellular calcium also can be released from the sarcoplasmic reticulum after hydrolysis of membrane phosphatidylinositol and subsequent formation of the secondary messenger inositol triphosphate (Robertson and Robertson, 1995). Intracellular calcium combines with calmodulin, which activates myosin light chain kinase (MLCK). Myosin light chain is phosphorylated, and the interaction between myosin and actin is promoted. Myosin and actin cross-bridging occurs, resulting in smooth muscle contraction. Cyclic AMP decreases MLCK and intracellular calcium, causing vascular smooth muscle to relax. Note that increasing cAMP in the vascular system causes relaxation, whereas contraction occurs in myocardial cells. Cyclic guanosine monophosphate (cGMP) also causes relaxation (Fig. 30–3). Endothelium-derived relaxing factor (EDRF; chemically related to nitric oxide) and endothelium-derived constricting factor (EDCF) are among the vasoactive substances (others include prostacyclin, histamine, and acetylcholine) released by the endothelial cell that control the hemodynamics of the cardiovascular system. Mediators such as EDRF released from the endothelial cell probably directly interact with vascular smooth muscle to cause hemodynamic effects. The intracellular response to EDRF (or nitric oxide) is probably signaled by cGMP. Not all vasoactive responses to the endothelium reflect EDRF or EDCF.

The Role of Nitric Oxide

For 20 years, researchers have attempted to identify a factor released from endothelial cells referred to as EDRF and responsible for relaxation in response to a number of vasodilator stimuli. Ultimately, nitric oxide (NO) was recognized to be the smallest and most basic mediator of vascular response (Whittle, 1995). It is released as a gas (and thus often is mistaken for nitrous oxide [NO$_2$] or "laughing gas") after synthesis from L-arginine. The reaction is stimulated by nitric oxide synthetase (NOS) (Fig. 30–4).

Two major classes and three isoforms of NOS have thus far been identified (Adams, 1996; Whittle, 1995; Parratt,

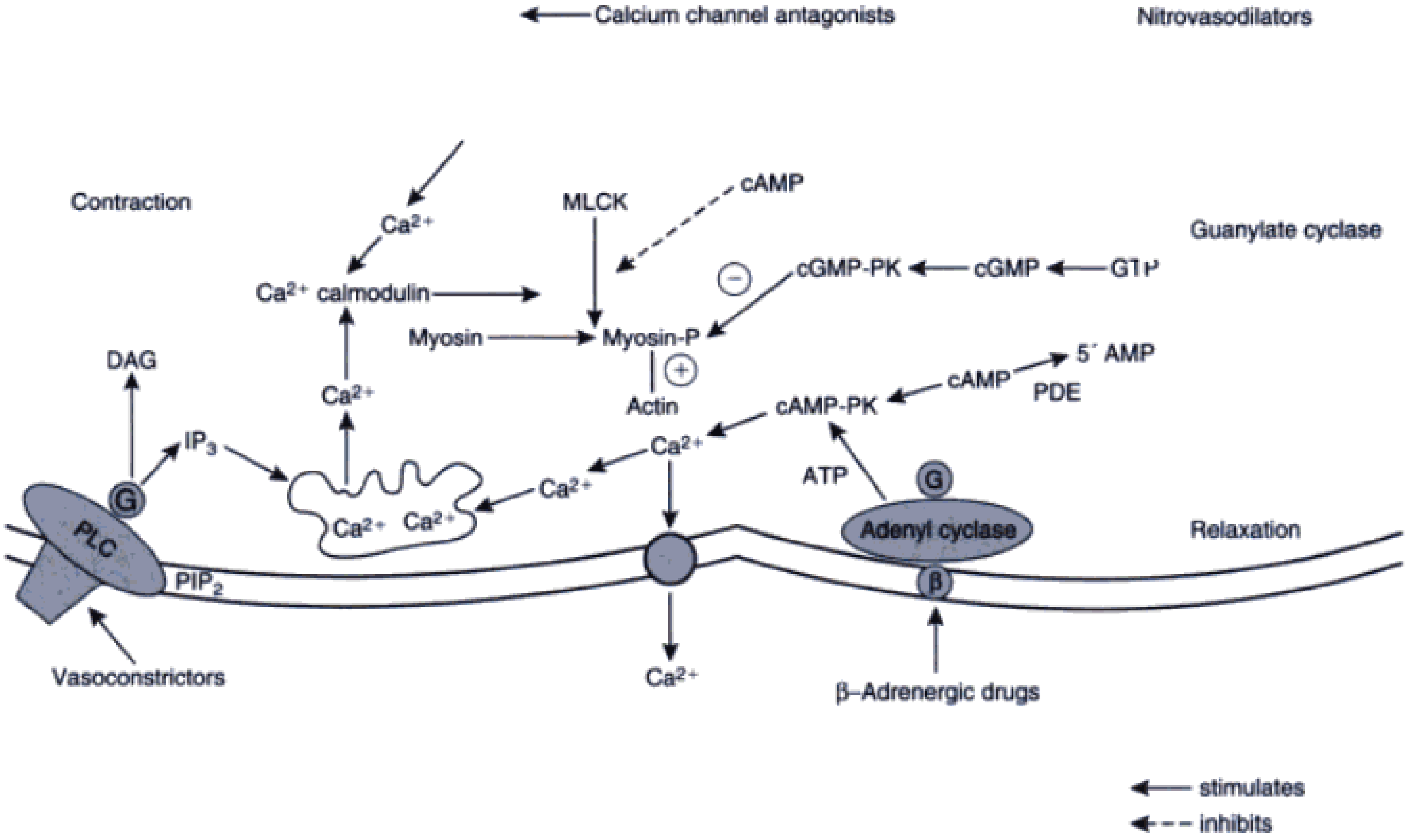

Figure 30–3. Contraction of vascular smooth muscle (vasoconstriction) reflects an influx of calcium, although mechanisms may differ from those in the myocardial cell. Calcium influx occurs through receptor-mediated channels or, less commonly, voltage-gated channels. Intracellular calcium combines with calmodulin. Myosin light chain kinase (MLCK) is activated, and myosin light chain is phosphorylated (Myosin-P), promoting the interaction between myosin and actin. Cyclic adenosine monophosphate (cAMP) appears to stimulate sequestration and efflux of intracellular calcium and through cAMP protein kinase (cAMP-PK) decreases MLCK, causing vascular smooth muscle to relax (an action opposite to that in the myocardial muscle cell). Cyclic guanosine monophosphate (cGMP) also causes relaxation, probably through nitric oxide–mediated mechanisms. Intracellular calcium also can be released from the sarcoplasmic reticulum after hydrolysis of membrane phosphatidylinositol (PIP$_2$) and subsequent formation of the secondary messenger inositol triphosphate (IP$_3$). ATP = adenosine triphosphate; DAG = diacylglycerol; GTP = guanosine triphosphate; PDE = phosphodiesterase; PLC = phospholipase C.

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Figure 30–4. Vasoactive mediators responsible for vasodilation (e.g., prostacyclin, histamine, acetylcholine) stimulate nitric oxide synthetase to convert L-arginine to nitric oxide (NO) in the endothelial cells. Nitric oxide enters the smooth muscle cell and stimulates guanylate cyclase such that cyclic guanosine monophosphate (cGMP) is released. ATP = adenosine triphosphate; cGMP-PK = cGMP-dependent protein kinase; GTP = guanosine triphosphate; Myosin-P = phosphorylated myosin.

1998). Constitutive NOS (cNOS or NOS-1) is continuously produced and includes two isoforms synthesized either by vascular endothelial cells (eNOS) or neurons (nNOS). Constitutive NOS is calcium dependent, and NO generated via this form tends to interact with cellular receptors in order to cause the response, which occurs rapidly. It is NO generated via cNOS that mediates response to vascular mediators such as acetylcholine, norepinephrine, histamine, and substance P. Inducible NOS (iNOS or NOS-2) is produced as needed by inflammatory cells (e.g., macrophages, neutrophils, and Kuppfer cells), generally after exposure to cytokines (e.g., tumor necrosis factor or interleukins) or bacterial lipopolysaccharides. Production of NO from iNOS requires new protein synthesis and is characterized by a delay of several (2 to 4) hours.

Nitric oxide causes its effect by diffusing across cellular membranes to intracellular targets. Cytosolic guanylate cyclase is a major intracellular messenger (Fig. 30–4) causing physiologic response to NO, such as dilation of blood vessels, inhibition of thrombogenesis, cytotoxic responses, and neuronal signaling. Additionally, because NO contains an unpaired electron in its outer orbit, it is a free radical and as such it has a short half-life and can contribute to the formation of other radicals. Yet, it also can serve as a scavenger of oxygen radicals. Nitric oxide is rapidly oxidized to nitrates and nitrites; these compounds are often measured as end products in lieu of NO because the latter has such a short half-life (Adams, 1996).

Despite its very short half-life, NO has many important and complex actions in the body. Under basal conditions, peripheral vasoconstriction is relieved by intermittent cNOS-induced NO in response to sheer stress and endothelial cell receptor stimulation. Inflammation and immune signals also induce NO release via iNOS. Nitric oxide inhibits platelet aggregation and adhesion, contributing to antithrombogenic mechanisms in the vascular endothelium. Modulation of inflammation varies, however, with cell type and the source of NO production (i.e., iNOS vs. cNOS). Although targeting NO production through drug therapy may appear to be a reasonable approach to the treatment of a variety of cardiovascular disorders, the complex nature of its release and the events leading to its release currently preclude predictable and safe modulation. It is likely, however, that selective modulation of NO ultimately will provide a therapeutic approach to many disorders.

PATHOPHYSIOLOGY OF CARDIAC DISEASE AS IT RELATES TO DRUG THERAPY: CONGESTIVE HEART FAILURE

Congestive heart failure (CHF) refers to the clinical manifestations that result from heart failure, including pulmonary and circulatory edema. Heart failure reflects the sequelae of neurohumoral responses that occur regardless of the underlying cause of heart failure (Francis, 1998). The responses are intended to compensate for loss of contractility or abnormal loading on the heart. Heart failure is considered compensated as long as cardiac output can be maintained in the normal range at rest or with limited exercise. Side effects caused by the compensatory mechanisms can, however, be serious. Cardiac failure becomes decompensated when cardiac output is no longer maintained despite marked compensatory mechanisms. As the heart fails, blood pressure decreases to the point that organ perfusion is compromised.

Compensatory mechanisms are implemented by the body in response to the inability of cardiac muscle to contract. These mechanisms reflect responses mediated by neural, hormonal, and renal mechanisms (Pool, 1997; Ruf-

sated for by increases in plasma catecholamines released from the adrenal gland. Myocardial contractility is directly increased. The failing heart, however, becomes increasingly dependent on circulating catecholamines. In the regional peripheral vasculature, α-adrenergic–mediated vasoconstriction ensures that arterial blood pressure will be preserved even at the cost of maintenance of cardiac output. Differential vasoconstriction among the vascular beds causes blood flow to be redistributed to organs with the highest metabolic requirements (i.e., brain, heart, and active skeletal muscles). The kidneys are among the organs whose blood flow is restricted, resulting in activation of the RAA system. Autoregulation of intrarenal blood flow (e.g., efferent renal arteriolar constriction) helps maintain glomerular filtration despite systemic redistribution. With progressive disease, catecholamine release in response to exercise can cause dramatic changes in regional circulation. Afterload increases, impairing ventricular emptying. Venoconstriction and fluid retention provide some compensation by increasing preload.

Although the goal of the compensatory mechanisms is to increase cardiac output, secondary effects frequently prove detrimental. Increased heart rate results in increased work and oxygen and energy needs. Persistent and significant elevation of systemic vascular resistance occurs due to the vasoconstriction mediated by angiotensin, circulating catecholamines, and other factors. Although elevation in resistance reflects an attempt by the body to increase organ perfusion, in fact it eventually becomes a major contributor to the ultimate deterioration of the failing heart. Increased resistance significantly increases cardiac afterload, and stroke volume decreases proportionately. The failing heart must work harder and use more oxygen to effect the same cardiac output. In addition to harder work, because stroke volume is less, the amount of blood in the heart during diastole is greater. Resistance is further mediated by vascular stiffness. Stiffness is caused by direct changes in the mechanical properties of vessels induced by intramural sodium and water content. Autoregulation of the vasculature is impaired, particularly in skeletal muscle.

Myocardial wall tension is also increased, and the heart cannot "relax" as it should during diastole. The heart receives its own blood supply and oxygen during diastole. Increasing left ventricular end-diastolic volume (and therefore tension) reduces the ability of the heart to meet its energy and oxygen needs. Elevated peripheral resistance thus represents a "vicious" cycle because it worsens the failing heart.

Vasoconstriction that accompanies CHF maintains systemic pressure in the normal range of 100 to 110 mm Hg. The maintenance of organ perfusion does not require systemic blood pressure of this magnitude. The brain, kidneys, and heart are the critical organs that will be effectively perfused at pressures 20 to 30 mm Hg less than normal. This "reserve" allows the use of agents that cause decreases in systemic blood pressure and thus afterload to the heart without compromising critical organ blood flow. In the face of reduced peripheral resistance, stroke volume can increase. In addition, in the presence of mitral insufficiency, the amount of blood regurgitated back through the mitral valve will also be reduced, which serves to lessen the volume overload to the failing heart. Finally, with reduction in volume overload, the end-diastolic volume of the left ventricle is reduced, wall tension is reduced, and myocardial perfusion increases.

In addition to activation of the neurohumoral and sympathetic nervous systems, the formation of reactive oxygen radicals has been associated with the development or progression of congestive heart failure (Ruffolo and Feuerstein, 1998a). Activation of transcription factors may lead to cardiac remodeling. Finally, recent evidence suggests that myocardial tissues undergoing remodeling are capable of locally producing corticosteroids (aldosterone and corticosterone). Indeed, spironolactone, a diuretic, inhibits angiogenesis, upon which collagen-producing myofibroblasts depend; spironolactone increases survival in human patients with advanced cardiac failure (Slight et al., 1999), suggesting another approach to therapy.

Drugs that are useful in the treatment of CHF include (1) afterload reducers; (2) preload reducers; (3) positive inotropes, particularly those that increase myocardial contraction without increased work load or oxygen demand; (4) negative chronotropes that slow the fast heart, allowing better perfusion of the heart and reducing its work load; and (5) drugs that help prevent sodium retention (Table 30–1).

Newer approaches to therapy may focus on slowing progression of the diseased myocardium (e.g., antioxidants, altered remodeling).

VASODILATOR THERAPY

Vasodilator drugs can be categorized according to the type of vessels that they dilate: arterioles (i.e., resistance vessels), veins (i.e., capacitance vessels), or both. Dilation of resistance vessels decreases afterload, whereas dilation of capacitance vessels decreases preload. Both decrease the workload of the heart.

Drugs that cause venodilation increase the volume of the capacitance vessels, thus reducing preload, or the blood volume returning to the right ventricle. Because stroke volume and diastolic ventricular volume are also determined by *preload* (i.e., the amount of blood entering the ventricle), drugs that reduce preload may also prove efficacious for the treatment of the failing heart. Reducing preload also reduces myocardial load and oxygen needs and increases myocardial efficiency. Preload reducers may also relieve some pulmonary vascular congestion. All three types of vasodilators can be useful in the patient with CHF.

Arterial Vasodilators

Recent literature suggests that the role of increased resistance in cardiac failure is much more important than previously thought. The inclusion of peripheral vasodilators in the armament of treatment for CHF, particularly in its early stages, has proved useful in reducing the dependency of digitalis for long-term treatment of these patients. Drugs that decrease peripheral resistance do so by dilating arterial or resistance vessels.

Table 30–1. Dosing Regimens of Cardioactive Drugs *(Continued)*

Drug	Dose	Route	Frequency
Lidocaine	4–8 mg/kg (D)	IV	Loading dose, then
	22–66 μg/kg (D)	IV infusion	1 min
	0.5–1 mg/kg (C)	IV	Loading dose, then
	10–20 μg/kg (C)	IV infusion	1 min
Lisinopril	0.25–0.5 mg/kg	PO	24 h
Melarsomine	2.5 mg/kg	Deep IM	24 h × 2 Rx
Metoprolol	0.5–1.0 mg/kg	PO	8–12 h
Mexiletine	5–10 mg/kg	PO	8–12 h
Milbemycin	0.25–1 mg/kg	PO	Once as microfilaricide
	0.5–1 mg/kg	PO	30 days as prophylaxis
	0.5–1 mg/kg (C)	PO	30 days as prophylaxis
Milrinone	0.5–1 mg/kg	PO	12–24 h
Moxidectin	3 μg/kg	PO	30 days as prophylaxis
Nadolol	5–10 mg (C)	PO	6–12 h
	40–60 (D)	PO	6–12 h
	0.25–0.5 mg/kg	PO	12 h
Nitroglycerin 2%	5–30 mm	Topical	4–12 h
	4–12 mg (max 15 mg)	Topical	6–8 h
	1/8–1/4 inch (C)	Topical	6–8 h
Nitroprusside	0.5–10 μg/kg (3 μg/kg) Use 50 μg dilution	IV infusion	1 min
Phenytoin	2–4 mg/kg up to 10 mg/kg (D)	IV	As needed
	10 mg/kg	IV	8 h
	30 mg/kg	PO	24 h
	2–3 mg/kg	PO	8–12 h
Prazosin	0.67 mg/kg (D)	PO	8–12 h
Prednisolone	1–2 mg/kg	PO	24 h for thromboembolism or pneumonitis associated with microfilariasis
Procainamide	2–20 mg/kg (D)	IV	Loading dose, over 30 min, then
	2–40 μg/kg (D)	IV infusion	1 min
	1–2 mg/kg (D)	IV	5 min
	1–2 mg/kg (C)	IV	Loading dose over 30 min, then
	10–20 μg/kg (C)	IV infusion	1 min
	6.6–22 mg/kg (D)	PO, IM	2–8 h
Propranolol	0.125–0.25 mg/kg (D)	PO	12 h
	0.2–1.0 mg/kg (D)	PO	8 h
	0.4–1.2 mg/kg (C)	PO	8–12 h
Ventricular arrhythmias	0.02–0.06 mg/kg	IV	over 2–3 min every 8 h
	0.44–1.10 mg/kg (D)	PO	8 h
	0.25–0.5 (C)	IV slowly	Loading dose
	2.5–5.0 mg total (C)	PO	8 h
Quinapril	0.5 mg/kg	PO	24 h
Quinidine	6.6–22 mg/kg	PO, IM	6 hr
	1–2 mg/kg, not to exceed 10 mg/kg	IV bolus	Cautiously, as needed
Taurine	250-300 mg	PO	24 h
Thiacetarsamide	2.2 mg/kg or 0.22 mL of commercial preparation/kg	IV	12 h × 4 Rx
Tocainide	5–10 mg/kg	PO	6–8 h
	6 mg/kg	IV bolus	Loading dose, then
	100 μg/kg	IV infusion	1 min†
Verapamil	0.05–0.15 mg/kg (up to 2 mg/kg if normal myocardial function)	IV infusion	10–30 min
	5–10 mg/kg (D)	PO	8–12 h
	1–3 mg/kg (D)	PO	6–8 h
	1.1–2.9 mg/kg (C)	PO	8 h

Abbreviations: C = cat; CPCR = cardiopulmonary cerebrovascular resuscitation; D = dog; D/W = dextrose in water; IM = intramuscular; IT = intratracheal; IV = intravenous; PO = oral; Rx = treatment; SC = subcutaneous.

*A fivefold increase in the IV dose is recommended when the drug is given IT to human patients.

†Dose established in experimental rather than clinical models.

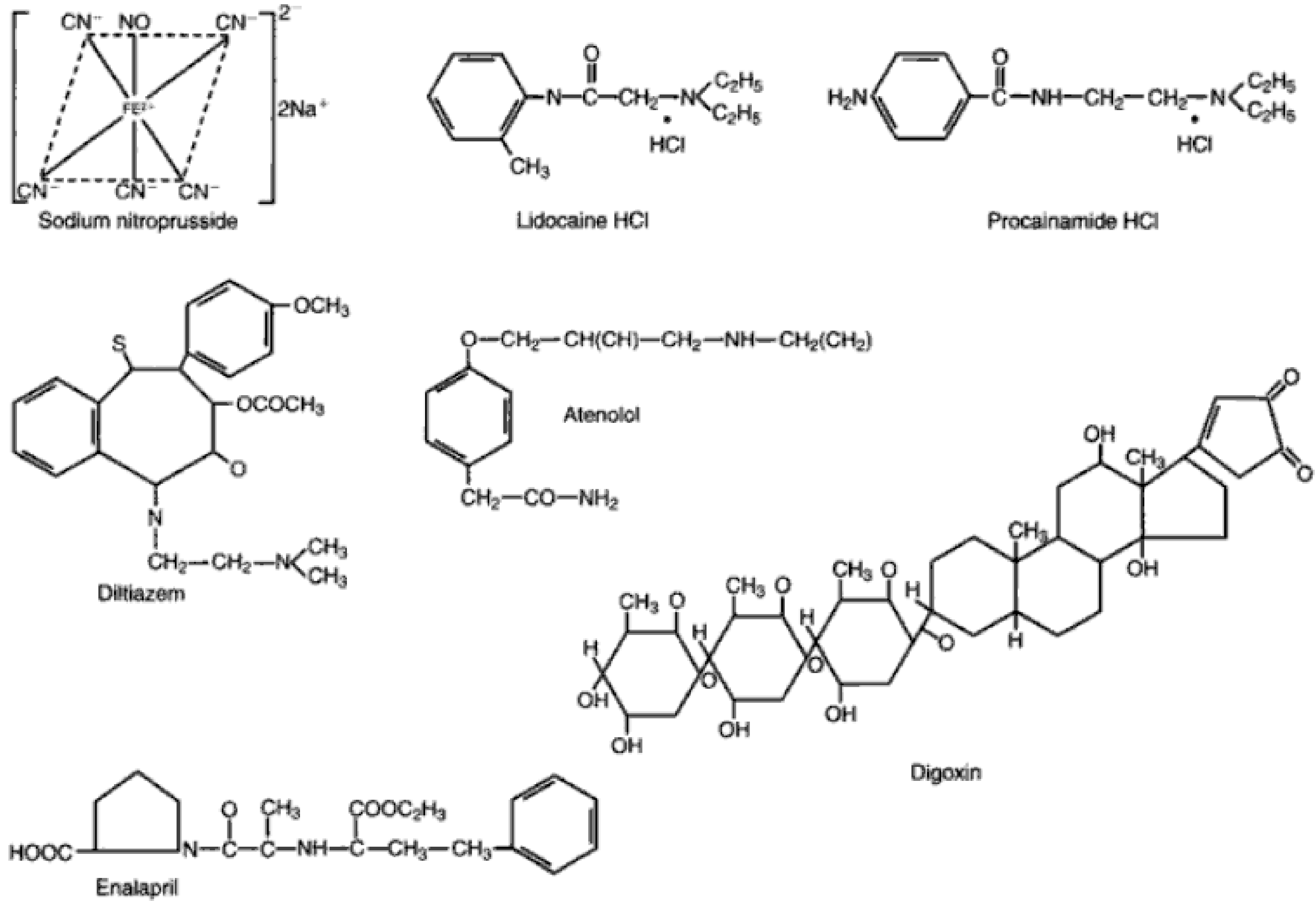

Figure 30-6. Structures of selected cardioactive drugs.

All three drugs are also available as oral preparations. Both verapamil and diltiazem are available as an intravenous solution for the rapid treatment of supraventricular arrhythmias.

Drug Interactions and Side Effects

The CCBs are involved in a number of drug interactions. Drugs that generally inhibit drug-metabolizing enzymes (e.g., cimetidine, chloramphenicol) will prolong the elimination and thus the cardiovascular effects. The CCBs also can prolong the elimination of drugs (e.g., cyclosporine, theophylline, and digoxin). The effects vary with the drug and are more likely with those CCBs that are eliminated by hepatic metabolism (e.g., diltiazem and verapamil). Side effects of the drugs vary with the primary pharmacodynamic effect. The major toxicities associated with CCBs are excessive vasodilation, negative inotropy, and depression of sinus nodal rate and atrioventricular conduction (negative chronotropy). Hypotension, bradycardia, and tachycardia (generally reflex) are the predominant clinical indicators. In patients with poor myocardial reserve, exacerbation of CHF may result in peripheral or pulmonary edema. Further clinical pharmacology and side effects may be addressed for specific drugs under the appropriate category.

Clinical Use

The use of CCBs for their peripheral vascular effects has been limited in veterinary medicine because of lack of efficacy. The recently approved human drug amlodipine, related to nifedipine, has, however, proved useful in the treatment of cats with hypertension and dogs with increased afterload but minimal compensatory mechanism. Like nifedipine, amlodipine affects predominantly smooth rather than cardiac muscle. Peripherally, amlodipine decreases total peripheral resistance. At doses causing vascular effects, amlodipine has little effect on sinus node function and cardiac conduction. Thus, a major advantage to amlodipine compared with other CCBs is that it may not cause reflex cardiac stimulation. Because its actions are independent of the renin-angiotensin–converting enzyme system, amlodipine should not be used as the sole afterload reducer in animals with myocardial failure associated with neural humoral compensatory mechanisms. Amlodipine is indicated for primary hypertension or that associated with renal disease. Other indications include afterload reduction in dogs whose myocardial failure has not responded or for those that have developed an intolerance to enalapril and diuretics. In human patients, a synergistic effect occurs when amlodipine or another peripherally acting CCB is combined with ACE inhibitors.

Amlodipine disposition has not been established for either dogs or cats. In humans, the drug undergoes minimal first-pass metabolism. When combined with other therapies, it should be used at a lower dose (see Table 30–1). To guide therapy, patients should be monitored with a targeted pressure of less than 150 mm Hg. Response should occur in 24 to 48 hours. Studies comparing the efficacy of amlodipine with enalapril in cats with primary hypertension or hypertension associated with renal disease are currently underway. The CCBs also are discussed as antiarrhythmics and negative inotropes.

Angiotensin-Converting Enzyme Inhibitors

Pharmacodynamic Effects

Because of their mechanism of action, ACE inhibitors do not only vasodilate. They also have important effects on the neurohumoral and renal compensatory responses associated with myocardial failure. They also appear to have primary cardiac effects. As such, they can be important in the management of any cardiac disease accompanied by CHF. The primary target of these drugs is the RAA system (see Fig. 30–6). Reduced perfusion of the kidneys, which accompanies decreased cardiac output in the failing heart, causes the release of renin from the kidneys into circulation. Renin causes the synthesis of angiotensin I, which in turn is converted to angiotensin II by ACE in the lungs. Angiotensin II is important in the pathogenesis of CHF because it initiates a series of events designed to maintain cardiac output. Blood volume increases due to the release of aldosterone and subsequent salt and water retention. Stroke volume can increase cardiac output. Angiotensin II also is a potent constrictor of resistance vessels, increasing systemic vascular resistance, which helps maintain blood flow to critical organs. Although initially these responses of the body to the failing heart are beneficial, eventually the effects become detrimental. Captopril, enalapril and other ACE inhibitors are highly specific inhibitors of the ACE. Circulating levels of angiotensin II and aldosterone are thus decreased. As a result of these effects, ACE inhibitors cause vasodilation (arterial), decreased systemic blood pressure, increased cardiac output, and reduced heart rate. Aldosterone secretion is reduced (not obliterated), and natriuresis (loss of sodium in urine) occurs. Some venodilation reduces preload as well, which may be of benefit.

The ACE inhibitors have a positive inotropic effect on the heart without an increase in heart rate. The mechanism is not clear, but for enalapril, it is associated with an increase in vasoactive intestinal peptide in the heart in rats (Duggan, 1998).

Three classes of ACE inhibitors have been developed for humans based on chemical structure: the sulfhydryl-containing drugs, which are structurally related to captopril; dicarboxyl-containing drugs related to enalapril (see Fig. 30–5) (including lisinopril, benazepril, and quinapril); and phosphorous-containing drugs related to fosinopril (Jackson and Garrison, 1995). Nine drugs are approved in the United States for use in humans. All appear equal in their efficacy of inhibiting RAA, with selection being based principally on which drug provides the best quality of life. Interestingly, captopril has improved quality of life in humans more than the other drugs (Jackson and Garrison, 1995).

Clinical Pharmacology

Many ACE inhibitors (e.g., enalapril and benazepril) are pro-drugs that require hepatic metabolism to an active state but are much more bioavailable than their active metabolites. Captopril and lisinopril are examples of ACE inhibitors that are not pro-drugs (Jackson and Garrison, 1995). As a group, the ACE inhibitors are eliminated via the kidneys. The risk of adverse reactions is greatly increased in the face of impaired renal function.

Captopril was used for dogs and cats before approval of enalapril for dogs. Captopril can induce positive hemodynamic effects within 1 hour, although the effects are short lived (4 hours) (Kittleson et al., 1993). Its half-life is short, and as such it must be given at 8-hour intervals compared with 12-hour intervals for enalapril. Enalapril is rapidly absorbed after oral administration. It is a pro-drug and requires conversion to the liver to its active metabolite, enalaprilat.

Clinical Use

The role of enalapril as a reducer of systemic peripheral resistance and for treatment of CHF associated with myocardial failure in dogs has been well established. Ettinger et al. (1998) established the beneficial effects of enalapril for dogs with either dilated cardiomyopathy or chronic vascular heart disease. Although the study was not well controlled for stage of disease or differences in conventional therapy, results supported the importance that ACE inhibition can have in improving the quality of life and, particularly in dogs with dilated cardiomyopathy, prolonging life (Ettinger et al., 1998). In their study of 110 dogs with acquired heart disease (primarily mitral insufficiency and dilated cardiomyopathy) Ettinger et al. (1998) found that mean time to treatment failure (including treatment with "traditional" cardiovascular drugs) increased from 77 days (placebo) to 156 days (enalapril). More dogs died suddenly in the enalapril treatment group; all but one, however, had pre-existing ventricular arrhythmias for which they were receiving antiarrhythmic therapy.

Controversy still exists over when ACE inhibitor therapy should be initiated, if and when it is the preferred vasodilator, and its position in the sequence of drugs used to treat myocardial disorders. For humans, ACE inhibitors are indicated for any patient with left ventricular systolic dysfunction even in the absence of clinical signs of overt cardiac failure (Jackson and Garrison, 1995). Studies in people further suggest that inhibition of ACE in patients with systolic dysfunction can prevent or delay the progression of heart failure, decrease the incidence of sudden death, and improve the quality of life (Jackson and Garrison, 1995). Ettinger et al. (1998) have offered treatment programs with enalapril based on the severity of disease.

The ACE inhibitors have been shown to have a protective effect in some cases of progressive renal disease (Jackson and Garrison, 1995). They can significantly reduce the loss of kidney function associated with diabetic nephropathy. Proteinuria may also be decreased by ACE inhibitors, perhaps due to changes in hydrostatic pressure or direct action on the glomerular membrane. Altering the selective permeability of the filtering membrane may reduce the exposure of mesangial cells to factors that stimulate proliferation. The progression of glomerular sclerosis also is thus offset. These findings have led to the suggestion that ACE inhibitors be tried in hypertensive patients that are at risk for developing end-stage renal failure (Jackson and Garrison, 1995).

Therapy with ACE-inhibitors should be closely monitored. Marked hypotension may occur with overuse of ACE inhibitors, particularly in animals treated with diuretics. To minimize negative sequelae of afterload reduction, treatment with enalapril should be initiated at a lower dose (O'Grady, 1995) (see Table 30–1) and increased in small increments at weekly intervals until clinical signs indicate improvement or further increases cannot be tolerated. The combined use of an ACE inhibitor with a diuretic such as furosemide can cause hyperkalemia in a small percentage of patients, particularly in the presence of dietary sodium restriction (Roudebush et al., 1994). To avoid hyperkalemia, potassium-sparing diuretics should not be used concurrently. Renal dysfunction may occur after the use of any ACE inhibitor (see Chapter 3). Captopril, enalapril (enalaprilat), and lisinopril cause relaxation of the renal artery (Fig. 30–7) (Malomvolgyi et al., 1995). For patients whose renal blood flow has been reduced, glomerular filtration may remain sufficient as the kidney self-regulates blood flow by constricting the efferent glomerular capillary. In the presence of an ACE inhibitor, however, the ability to self-regulate renal blood flow may be lost. Glomerular filtration subsequently may decrease, particularly if cardiac function does not sufficiently improve to compensate for the loss of hydrostatic pressure associated with decreased renal blood flow (Jackson and Garrison, 1995). Animals that have been treated with aminoglycosides, nonsteroidal agents, or other drugs that alter humoral regulatory mediators in the kidney are predisposed to ACE inhibitor-induced renal dysfunction (see Chapter 28). Renal function should be monitored weekly for the first month of therapy in patients predisposed to adverse renal effects (O'Grady, 1995). Proteinuria can be induced by ACE inhibitors, but proteinuria is not a contraindication for ACE inhibitor use. The ACE inhibitors reportedly cause a dry cough in up to 20% of human patients. The mechanism is not known, but the cough resolves when therapy is discontinued (Jackson and Garrison, 1995). The ACE inhibitors should not be used in pregnant animals.

Other Angiotensin-Converting Enzyme Inhibitors

Lisinopril is a renally eliminated ACE inhibitor approved for human use. In contrast to enalapril, lisinopril requires no pro-drug activation by the liver. Its elimination is impacted only with marked decrease in glomerular filtration rate. Indications for animals include liver disease. Another advantage is that it can be given once daily (see Table 30–1). Benazepril (approved for use in dogs in Canada) and its active metabolite benazeprilate offer another example. The metabolite is much more active than the parent drug. In contrast to other ACE inhibitors, the newer ACE inhibitors are not renally excreted. Quinapril is an ACE inhibitor available outside of the United States. It is available as a 5-mg tablet, which is convenient for accurate dosing. It also can be administered once daily (see Table 30–1) (Morisse and Kersten, 1995).

Arterial and Venous Dilators

Organic Nitrates

Organic nitrates activate cGMP, which ultimately decreases actin and myosin interaction. All vascular smooth muscle is relaxed. Nitrates and nitrates cause arterial and venous smooth muscle dilation. In addition, they directly dilate coronary vessels. At low concentrations, venular dilation predominates, and net systemic vascular resistance is usually not affected. Pharmacologic effects occur very rapidly. First-pass metabolism limits the use of these drugs to intravenous, sublingual, and topical (ointment) administration.

Nitroglycerin is not a nitro compound as its name suggests but is a member of the organic nitrate group. Although nitrates relax all smooth muscle, the dose of nitroglycerin used is intended to cause predominantly venous dilation and preload reduction. Pulmonary and systemic congestion and myocardial workload are reduced. Nitroglycerin is available for intravenous and sublingual use and as an ointment. The 2% ointment form is the most commonly used preparation in veterinary medicine. It can be applied to the hairless portion of an animal's skin (abdomen or ear). Gloves should be used by the caregiver to avoid percutaneous absorption of drug. The clinical indication for use is limited to acute (emergency) treatment of CHF.

Sodium Nitroprusside

Nitroprusside (see Fig. 30–6) is included in the group of nitrovasodilators (Oates, 1995). Inside smooth muscle cells, it is metabolized to NO, which in turn activates cGMP and subsequently vasodilation (see Fig. 30–3). The NO system that activates nitroglycerin is different from that activating nitroprusside, accounting for differences in vascular beds targeted by each drug (Oates, 1995). Both arteries and venules are dilated by nitroprusside. Nitroprusside is one of the most potent vasodilators available. The advantages of nitroprusside over other vasodilator drugs include its potency, its effect in both preload and afterload reduction, immediate hemodynamic effects, extremely short half-life, and low cost. The major disadvantage is that it must be administered by constant intravenous (IV) infusion. The potential for hypotension necessitates close monitoring. The drug is useful for the emergency treatment of severe CHF.

Prazosin

Prazosin is an α-adrenergic receptor blocker. Prazosin is also a venous dilator (perhaps due to inhibition of cAMP), however, and is thus considered by many to be both a preload and afterload reducer. Despite significant first-pass metabolism, prazosin is effective after oral administration,

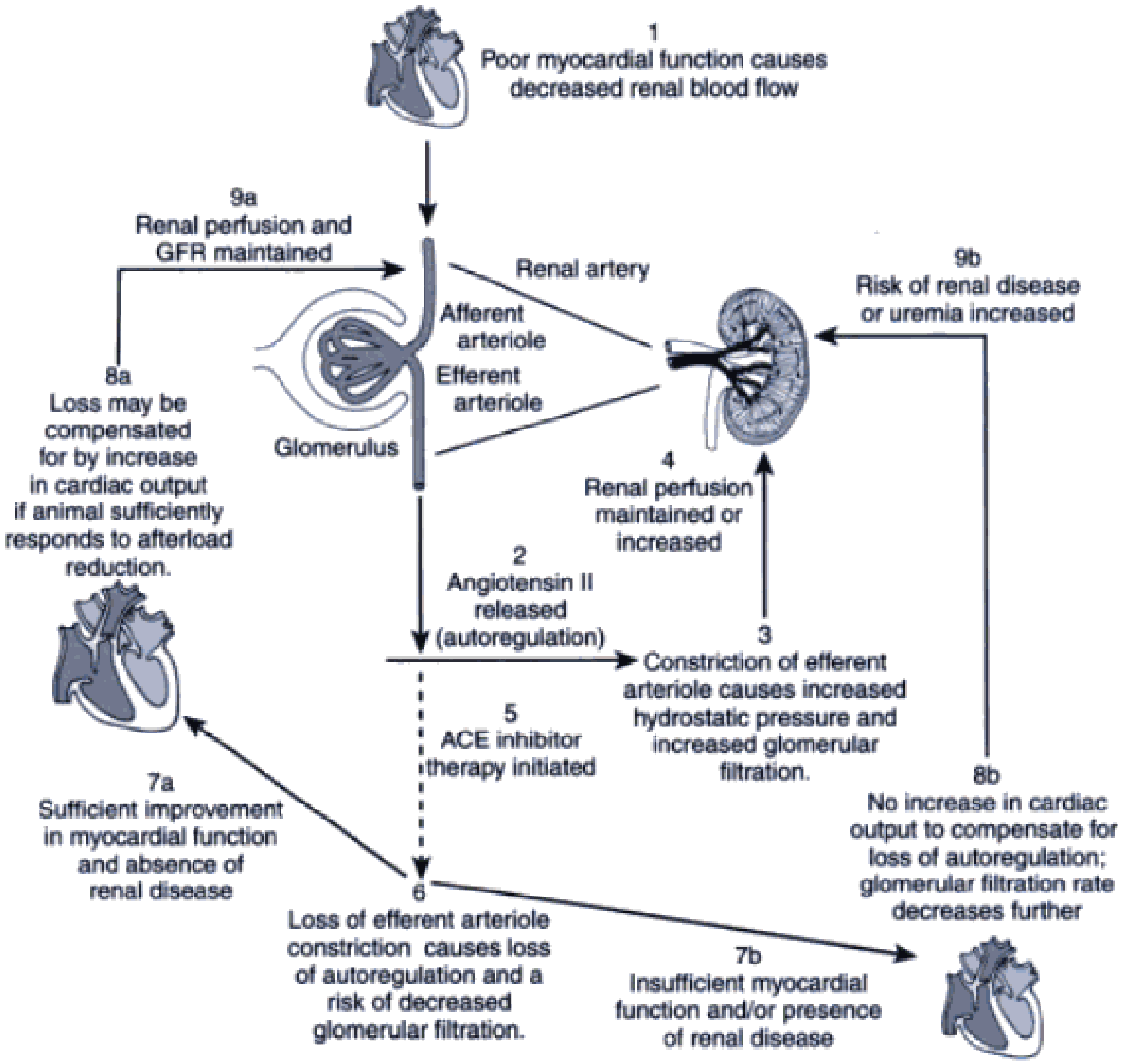
1
Poor myocardial function causes decreased renal blood flow
9a
Renal perfusion and GFR maintained
Renal artery
9b
Risk of renal disease or uremia increased
Afferent arteriole
Efferent arteriole
Glomerulus
8a
Loss may be compensated for by increase in cardiac output if animal sufficiently responds to afterload reduction.
4
Renal perfusion maintained or increased
2
Angiotensin II released (autoregulation)
3
Constriction of efferent arteriole causes increased hydrostatic pressure and increased glomerular filtration.
5
ACE inhibitor therapy initiated
7a
Sufficient improvement in myocardial function and absence of renal disease
8b
No increase in cardiac output to compensate for loss of autoregulation; glomerular filtration rate decreases further
6
Loss of efferent arteriole constriction causes loss of autoregulation and a risk of decreased glomerular filtration.
7b
Insufficient myocardial function and/or presence of renal disease

Figure 30–7. Despite their kidney-sparing effects in patients with glomerulonephritis, angiotensin-converting enzyme (ACE) inhibitors may contribute to renal disease in patients whose renal blood flow is threatened. In such patients, maintenance of glomerular filtration may depend on increased efferent arteriolar tone (vasoconstriction). Use of ACE inhibitors reduces this tone. In patients whose cardiac function is sufficient (including those that respond to decreased afterload), increased cardiac output can compensate for decreased efferent arteriolar tone, thus maintaining glomerular filtration rate. In patients that are sodium depleted or have severe myocardial dysfunction, glomerular filtration rate may decline. Dashed line = inhibited.

but tolerance develops rapidly. Prazosin is an effective antihypertensive agent. It is more effective when used in combination with other drugs. Prazosin is probably not used clinically because hydralazine affords a much better reduction in peripheral resistance and increase in cardiac output.

Nitroglycerin

Nitroglycerin (glyceryl trinitrate), as with other organic nitrates, is both an arterial and venous dilator. It is often, however, cited as only a venodilator, acting on capacitance vessels (Spargo et al., 1987). The difference in arterial versus venodilation may reflect use in doses low enough to cause venous but not arterial dilation.

ANTIARRHYTHMIC DRUGS

Cardiac Arrhythmias

Heart rate is determined primarily by the rate of diastolic depolarization (slope of phase 4), which in the normal heart, is under autonomic control. Acetylcholine (released from parasympathetic nerves) slows or decreases and norepinephrine (released from the adrenal cortex) increases the heart rate, respectively. As heart rate increases, stroke volume decrementally decreases, and cardiac output may decrease. Cardiac arrhythmias arise from abnormalities of automaticity (impulse initiation) or conduction (impulse propagation), or both. Automaticity will be accelerated in any tissue when the rate (or slope) of phase 4 depolarization increases. An increase in automaticity will either increase the heart rate or allow the emergence of ectopic foci (i.e., pacemakers that normally would be latent). If the frequency of the latent pacemaker exceeds that of the sinoatrial node, premature or ectopic beats or tachyarrhythmias may occur. Drugs that decrease automaticity do so by decreasing the rate of phase 4 spontaneous depolarization. This results in the suppression of ectopic foci and allows the sinoatrial node to resume its dominance. Automaticity can also be reduced by drugs that increase the excitation threshold or the diastolic membrane potential (i.e., increase the negativity). Either of these two mechanisms would lengthen the time needed to attain threshold potential. Finally, spontaneous discharge can be reduced by increasing the action potential duration (Roden, 1995).

Many arrhythmias result from conduction abnormalities

Class I Antiarrhythmic Drugs

Class I agents comprise the standard membrane-stabilizing drugs such as lidocaine, quinidine, and procainamide. These agents work by selectively blocking the fast Na^+ channels and depressing phase 0 of the action potential. This is caused by a direct membrane-stabilizing or "local anesthetic" effect. The decrease in phase 0 depolarization results in decreased conduction velocity. In addition, the Class I drugs increase the threshold of excitability and decrease the rate of spontaneous phase 4 depolarization, thus reducing the emergence of ectopic foci. The effect of these agents on automaticity and generation of ectopic foci seems to be more prevalent than the effects on conduction velocity. Some of these drugs also prolong the duration of the cardiac action potential, especially the effective refractory period, and are useful in treating re-entrant arrhythmias (Anyukhovsky et al., 1997). In general, the antiarrhythmic effects of Class I drugs occur in dogs with concentrations similar to those in people (Hashimoto et al., 1983).

Class I agents can be further subdivided based on their effects on the refractory period and on the rate of repolarization. Class IA drugs include quinidine, procainamide, and disopyramide. These agents reduce the rate of phase 0 depolarization. Because they prolong both the effective refractory period and the action potential duration, they also delay repolarization.

Quinidine

Quinidine is related to the antimalarial drug quinine. It blocks open Na^+ and multiple K^+ currents. Sodium blockade results in increased threshold of excitability and decreased automaticity. The QRS duration increases and the QT interval may also be prolonged. Blockade of K^+ channels prolongs action potentials, especially at slow rates (Roden, 1995). It affects most types of cardiac muscles (Roden, 1995; Adams, 1995a). It has a broad spectrum of efficacy against supraventricular and ventricular arrhythmias. Quinidine suppresses ectopic pacemakers. Because it also prolongs the effective refractory period, it is useful in the treatment of re-entrant arrhythmias (Anyukhovsky et al., 1997; Sosunov et al., 1997), and this pharmacologic effect may represent its major clinical effectiveness. In the atria, quinidine also has indirect, antivagal ("atropine-like") effects. Its ability to prolong atrial refractoriness probably accounts for its ability to interrupt atrial re-entrant rhythms (atrial fibrillation).

Quinidine sulfate is absorbed rapidly after oral administration (Roden, 1995; Adams, 1995a). The gluconate form is absorbed more slowly. It can be given intramuscularly (IM), but this route is painful. It is 90% protein bound. Distribution is rapid to most tissues. The volume of distribution is large (2 to 3 L/kg). Quinidine is metabolized by the liver and excreted in the urine. The half-life is about 6 hours. There is considerable patient variation in metabolism, necessitating individualized therapy. Although quinidine can be given IM or IV, its practical use is limited to oral (PO). As a broad-spectrum drug, it can be used effectively for acute and chronic treatment of supraventricular and ventricular arrhythmias. It can be used for the treatment of digitalis intoxication but may not be preferred because it can exacerbate the abnormalities of cardiac rhythm induced by digitalis by altering digoxin binding to cardiac tissue and increasing plasma concentrations of the glycoside, although this effect is controversial (Colvin et al., 1990). The duration of action of quinidine may be shortened by drugs that increase microsomal enzymes. Cardiotoxicity may result in arrhythmias such as atrioventricular blockade or ventricular arrhythmias (Roden et al., 1986). Sudden death due to syncope has been reported.

The atropine-like effects of quinidine probably account for part of its potentially serious side effects. Vagal tone is important in controlling conduction in the atrioventricular node, and the loss of this control due to quinidine may result in increased impulse conduction to the ventricles. This effect is referred to as *paradoxical acceleration.*

Quinidine is also an α-adrenergic blocking agent and can cause vasodilation. Finally, gastrointestinal symptoms (nausea, vomiting, and diarrhea) may occur, particularly with the sulfate form. Daily doses range from 5 to 15 mg/kg; therapeutic concentrations are 2 to 6 μg/mL. The drug can be given IV with extreme caution.

Procainamide

Procainamide differs from procaine only by replacement of an ester with an amide (see Fig. 30–6). Procainamide blocks open Na^+ channels and outward K^+ channels. Thus, it decreases automaticity, increases refractory periods, and slows conduction as well as prolongs the action potential duration. Its *N*-acetyl metabolite does not block Na^+ channels but does prolong the action potential duration (a K^+-blocking effect) (Roden, 1995). The effects of procainamide on automaticity, excitability, responsiveness, and conduction are the same as those of quinidine. Its indirect effects (those effecting the autonomic nervous system) are significantly weaker. It does not cause α-adrenergic blockade or paradoxical acceleration (Roden, 1995).

Procainamide is rapidly and almost completely absorbed after oral administration. Peak concentrations are attained within 45 to 75 minutes if a capsule is given; tablets take longer. Bioavailability in the dogs approximates 85% (Papich et al., 1986a). Only about 20% of the drug is protein bound in people (Roden, 1995). Distribution is to most tissues except the brain (Roden, 1995), and the apparent volume of distribution is large (1.44 L/kg in dogs) (Papich et al., 1986a). Procainamide is extensively biotransformed by the liver to metabolites. *N*-acetylprocainamide is a major metabolite of procainamide that is formed in humans. The metabolite is equal in efficacy but less potent than the parent compound in the control of ventricular arrhythmias (Bagwell et al., 1976). The formation of *N*-acetylprocainamide is not as great in the acetylation-deficient dog (Papich et al., 1986a). The half-life of procainamide in the dog is 2.5 to 2.8 hours. Mean concentration necessary to control arrhythmias in quabain-intoxicated dogs is 33.8 μg/mL, with a range of 25 to 48.5 μg/mL (Papich et al., 1986b). These concentrations are higher than those recommended for people, probably reflecting the absence of the active metabolite in dogs.

The drug is available as oral capsules and tablets for chronic use; sustained-release tablets are also available.

Intravenous preparations are available for acute or unstable situations. Hypotension can occur if an initial loading dose is given as a rapid bolus. Rapid IV infusion administration is a reasonable approach for the treatment of the acute patient. Procainamide can also be administered IM (15 to 20 mg every 2 hours [dog] or 8 to 16 mg every 3 to 6 hours). When making the transition from IV to PO dosing, the infusion should be stopped, and about one drug elimination half-life should elapse before administration of the first oral dose (125 to 500 mg every 6 to 8 hours, a total of 33 mg/kg per day). Toxicosis is indicated by a 50% widening of the QRS complex or by bradyarrhythmias or tachyarrhythmias.

Procainamide is a broad-spectrum antiarrhythmic drug. In general, its effectiveness as a ventricular antiarrhythmic drug parallels or exceeds that of quinidine, and it is useful for patients who have failed quinidine therapy. Arrhythmias for which procainamide have proved useful include ventricular (Davis et al., 1982) and, to a lesser degree, supraventricular. Procainamide can suppress digitalis-induced toxicity but fatalities may occur. Toxicities include (1) cardiotoxicity, similar to that induced by quinidine; (2) hypotension with rapid IV administration (bolus); and (3) gastrointestinal signs (anorexia, nausea, vomiting, diarrhea).

Disopyramide

Disopyramide is the newest Class IA drug. Its pharmacologic effects and spectrum of activity are similar to those of procainamide and quinidine. Although it is effective in controlling supraventricular arrhythmias, its primary use is for ventricular tachyarrhythmias. Disopyramide has been studied in the dog (Cook et al., 1990). It is quickly absorbed after oral administration, but it undergoes rapid metabolism and clearance. Its half-life is less than 2 hours in the dog, necessitating multiple daily administrations. Disopyramide has potent antivagal effects and can therefore increase the ventricular rate dramatically in patients with supraventricular tachycardias. More importantly, disopyramide also has a negative inotropic effect on the heart and can be lethal for patients with pre-existing myocardial disease. Clinical indications for disopyramide are probably limited by its potential adverse affects on the heart (Schmidt et al., 1992).

Class IB Drugs

Class IB drugs include agents such as lidocaine and phenytoin. Lidocaine (see Fig. 30–6), widely used as a local anesthetic, also is the prototypic Class IB drug. It differs markedly from Class IA drugs pharmacokinetically and pharmacodynamically. Class IB drugs are distinguished from class IA drugs because they (1) do not affect phase 0 depolarization and conduction velocity in normal tissue and (2) accelerate repolarization and thus shorten the effective refractory period and action potential duration. The actions of lidocaine reflect preferential binding to sodium channels that are open (or active, occurring during phase 0) or refractory (or inactivated, during phases 1 through 3) as opposed to resting channels (phase 4). Lidocaine is thus more effective in cardiac tissues with a long action potential duration (i.e., depolarized for a longer than normal period of time such as occurs with ischemia) and less effective in atria or normal ventricular myocardium. The action potential duration is shortened more than the effective refractory period, however, and the net effect is a *prolonged* effective refractory period compared with the action potential duration. Lidocaine minimally affects the sinoatrial node, atria, or atrioventricular node. In the ventricles, it suppresses normal automaticity in the Purkinje fibers and delays impulse conduction in the ventricular muscle. Because the effects depend on potassium, hypokalemia minimizes efficacy. Lidocaine also increases the ventricular fibrillation threshold and may decrease the risk of acute death associated with ventricular fibrillation.

Lidocaine is well absorbed orally, but it is subject to first-pass metabolism, and only one third of the drug reaches systemic circulation. Peak concentrations in dogs after IV administration of 6 mg/kg approximate 10 μg/mL (Wilcke et al., 1983a); at 3 hours concentrations are 0.1 μg/mL. Absorption is complete after IM administration. After IM administration, peak concentrations approximate 1.8 μg/mL at 30 minutes. Distribution is rapid. The volume of distribution is large (1.44 L/kg) (Wilcke et al., 1983a). About 70% is protein (glycoprotein) bound. Hepatic metabolism to active and inactive metabolites is complete. The elimination half-life in dogs approximate 50 minutes (Wilcke et al., 1983a). Lidocaine is considered a "flow-limited" drug; hepatic clearance is so rapid that measurement of plasma concentrations (or the appearance of its metabolite) have been used to evaluate hepatic function in people and experimentally in dogs. Severe liver disease and reduced blood flow to the liver reduces the rate of metabolism. Lidocaine is prepared for IV administration; no other drugs are added to the solution prepared for cardiac arrhythmias. Lidocaine can be administered IV as a rapid bolus or as a continuous IV infusion. It can also be given IM in emergency situations.

The use of lidocaine as an antiarrhythmic drug is predominantly for emergency treatment of ventricular arrhythmias. Its pharmacologic effect occurs very rapidly, and the drug can be safely administered IV in the dog. The cat is more likely to develop toxicity. Lidocaine has minimal effects on the autonomic system. Lidocaine can counteract arrhythmias in the abnormal Purkinje system and ventricles without affecting normal cardiac tissues. Lidocaine can therefore abolish ventricular re-entrant rhythms. Therapeutic and toxic lidocaine concentrations have been established experimentally (six dogs) (Wilcke et al., 1983b). Minimum effective concentrations for experimentally induced quabain toxicity (eradication of ventricular tachycardia) ranged from 3.8 to 7.65 μg/mL (mean 6.25 μg/mL). The time necessary to eradicate the arrhythmia ranged from 0.3 to 1 hour after infusion of 1480 mg/h (Wilcke et al., 1983b). Neurologic manifestations of toxicity appeared at 6.3 to 10.4 μg/mL (mean 8.21 μg/mL) (tonic extension) and increased (cortical seizures) at 7.3 to 11.2 μg/mL (mean 9.58 μg/mL). Other neurologic manifestations of lidocaine toxicity include anxiety, sedation, and disorientation.

Therapeutic indications for lidocaine are limited almost exclusively to ventricular arrhythmias because it is such a narrow-spectrum drug. Drug interactions are limited. Basic drugs can compete with lidocaine for binding sites on glycoproteins. Lidocaine has few undesirable effects. The primary toxicity in the dog occurs in the central nervous system (CNS) with symptoms that range from drowsiness or agitation to muscle twitching and convulsions at higher plasma concentrations (see discussion of local anesthetics). The cat is prone to cardiac toxicity (suppression). Lidocaine can worsen first-degree or second-degree atrioventricular block and is contraindicated for patients with third-degree heart block because of suppression of ventricular automaticity. A large IV bolus may cause sinus arrest; cats are more prone to this adversity.

Tocainide is a Class IB antiarrhythmic drug that is similar in chemistry to lidocaine. The mechanism of action is also similar. A major difference, however, is that tocainide does not undergo first-pass metabolism, and thus oral bioavailability is 100%. As such the drug can be administered chronically for long-term management of ventricular arrhythmias, particularly those that responded to lidocaine. Tocainide also may be useful for treatment of ventricular arrhythmias that fail procainamide. It is often not useful, however, for those that are refractory to lidocaine. Tocainide has been studied in dogs with experimentally induced myocardial infarction (Wallace et al., 1991). After IV administration, spontaneous premature ventricular complexes were reduced. Mexiletine, like tocainide, is a structural analogue of lidocaine. Both mexiletine and tocainide are more likely than lidocaine to cause CNS and gastrointestinal toxicity. In addition, blood dyscrasias have occurred in dogs (Muir, 1991). Contraindications to lidocaine should be followed for mexiletine and tocainide.

Phenytoin is an anticonvulsant that has a limited spectrum of antiarrhythmic activity in the heart. It is considered to be a Class IB drug, and therefore its activity in the heart is similar to that of lidocaine. Its primary usefulness in veterinary medicine is for the management of digitalis-induced arrhythmias because it significantly shortens atrioventricular nodal and Purkinje refractory period in digitalized patients.

Class IC Drugs

Class IC drugs cause effects similar to those of the Class IB drugs except that they do not prolong the refractory period. Conduction velocity is depressed; propafenone also causes β-blockade. These drugs, including encainide, flecainide, and lorcainide, are currently being studied.

Class II Antiarrhythmic Drugs

Class II antiarrhythmic drugs are the β-adrenergic receptor blocking agents. Although discussed as antiarrhythmic drugs, they also have effects that reflect actions other than decreased heart rate. Discontinuation of β-blockade has been associated with rebound effects in humans, leading to a worsening of heart failure and arrhythmias. Down titration (decreasing the dose as the drug is discontinued) reduces the rebound effects (DiLenarda et al., 1999).

β-Blockers decrease the magnitude of Ca^{2+} current, heighten its inactivation, and decrease the magnitude of potassium and chloride currents. They also decrease pacemaker current and thus sinus rate (Roden, 1995). Although discussed as antiarrhythmics, a number of clinical trials have revealed their efficacy in the treatment of heart failure.

Nonselective β-Blockers

Propranolol is the prototype β-blocker. It is a competitive, nonselective β-blocker that blocks both β_1-receptors and β_2-receptors. Propranolol is most effective in the presence of elevated sympathetic tone. β-Blockers increase AV nodal conduction and prolong AV nodal refractoriness and thus may be useful for re-entrant arrhythmias associated with the AV node (Roden, 1995). Propranolol exhibits a negative chronotropic effect in conditions of supraventricular tachycardia, particularly if the source of the tachycardia is due to elevated levels of catecholamines (e.g., *not* hypokalemia, fever, some heart diseases). Propranolol is rarely able to convert a supraventricular arrhythmia to a normal sinus rhythm. It will slow ventricular rates in patients suffering from supraventricular arrhythmias, however, including those induced by digitalis toxicity. In acutely ischemic myocardial tissue, β-blockers increase the energy necessary to fibrillate the heart and thus may decrease mortality (in humans) of chronic therapy following myocardial infarct (Roden, 1995). As a β_1-blocker, propranolol is also a negative inotrope. This pharmacologic effect can be detrimental in the patient with small cardiac reserve (e.g., the patient with CHF). Propranolol has been studied in erythroid and hyperthyroid cats (Jacobs et al., 1997). Changes in disposition induced by hyperthyroidism suggest that a lower dose is indicated for oral administration because of increased bioavailabity.

Clinical indications of propranolol as an antiarrhythmic include reduction of ventricular rate in cases of supraventricular tachycardias, hypertrophic and other forms of obstructive heart disease, and hyperthyroidism.

The toxic effects of propranolol are the result of β-blockade and include bradyarrhythmias, hypotension, heart failure, bronchospasm, and hypoglycemia, particularly in diabetics. One should be particularly cautious in administering a β-blocker to a patient with little myocardial reserve. In an intact experimental canine model, insulin (4 IU/min IV with glucose) was shown to be superior to epinephrine for treatment of acute propranolol toxicity (Kerns, 1997). Nadolol (5 to 10 mg orally every 6 to 12 hours [cat]; 40 to 60 mg orally every 6 to 12 hours [dog]) also is a nonspecific β-blocker that is renally excreted. Side effects and contraindications typical of propranolol occur for nadolol (Muir, 1991).

Selective β-Blockers

Carvedilol represents the newest (third) generation of β-blockers. Although it is characterized by beta β_1 and β_2 as well as adrenergic blockade, it is relatively (mildly) β_1-selective in human patients. As such, it decreases total peripheral resistance and preload without compromise of cardiac output or reflex tachycardia (Ruffolo et al., 1995b). It is the only β-blocker approved for use in the treatment of heart failure in human patients. Advantages compared with traditional selective β-blockers such as metaprolol include reduced mortality in human patients with left ventricular failure, perhaps due to a more complete antagonism of sympathetic activation (DiLenarda et al., 1999; Ruffolo et al., 1998b; Sanderson et al., 1999; Kotsinas et al., 1999; Francis, 1998). Its benefits do not reflect a reduction in heart rate as much as improvement in left ventricular function. Additional advantages may include antioxidant and antiproliferative properties and may inhibit apoptosis in the heart (Feuerstein et al., 1998; Ruffolo et al., 1998b). Finally, carvedilol may inhibit the synthesis of endothelin in coronary arteries (Ohlstein et al., 1998). Carvedilol appears to protect against doxorubicin-induced cardiomyopathy (Matsui, 1998). The drug has been studied in dogs but apparently not in cats.

Carvedilol is well absorbed in dogs and undergoes extensive hepatic metabolism, including glucuronidication and subsequent biliary excretion (Schaefer, 1998). The kinetics and selected pharmacodynamics have been studied in anesthetized dogs (Sawangkoon et al., 2000). The elimination half-life was 54 minutes (compared with 2.4 hours in humans) and the volume of distribution was 2 L/kg. When studied at doses ranging from 10 μg to 630 μg/kg, heart rate did not decrease, although these authors report that other investigators have observed an increased heart rate in awake dogs. Pulmonary and systemic pressures decreased in treated animals but increased in control animals, consistent with the α-blockade effect of the drug. The authors recommend an optimal plasma drug concentration of 100 ng/mL, achieved after IV infusion of 150 to 310 μg/mL.

The efficacy of carvedilol and metoprolol for the treatment of chronic heart failure has been compared and also studied versus standard therapy in humans (Sanderson et al., 1999; Kukin et al., 1999). No difference could be detected in most outcome measures between the two treatments, although patients receiving carvedilol had lower blood pressures compared with those receiving metoprolol. Patients receiving either drug significantly improved compared with those receiving standard therapy (Sanderson et al., 1999). In a rabbit model of ischemia, carvedilol provided superior cardioprotection, probably due to antioxidant and antineutrophil effects (Feuerstein et al., 1998).

Atenolol (see Fig. 30–6) is a selective β_2-blocker indicated for cats with hypertrophic cardiomyopathy associated with outflow obstruction and respiratory distress. Atenolol is 90% bioavailable after oral administration in normal adult cats (Quinones et al., 1996). Elimination half-life in normal adult cats is 3.44 ± 0.5 and 3.65 ± 0.39 hours after IV and PO administration, respectively. A dose of 3 mg/kg orally generates a peak plasma concentration of 0.48 ± 0.16 μg/mL and will block cardioresponsiveness to isoproterenol for 12 but not 24 hours, suggesting a 12-hour dosing interval.

Esmolol is a β_1-selective blocker characterized by a very (ultra) short half-life and a duration of effect of about 10 minutes. It is administered IV and has proved useful for acute ventricular arrhythmias associated with inhalation anesthesia and surgical removal of hyperactive thyroid glands (Muir, 1991).

Metoprolol is a relatively selective β_1-blocker. A large multicenter clinical trial studied its use for treatment of dilated cardiomyopathy compared with a placebo. The drug did not appear to decrease mortality but did improve ventricular function as well as quality of life.

Class III Antiarrhythmic Drugs

Class III drugs prolong the cardiac action potential and refractory period. They have no effect on the fast Na^+ conductance and do not cause β-blockade. There are two members of this class: bretylium and amiodarone.

Bretylium is used as an antifibrillatory drug in humans. It accumulates in sympathetic nerve terminals, where it blocks norepinephrine release, but only after an initial release of stored neurotransmitter. It is, however, minimally effective in dogs. It affects primarily the Purkinje fibers and ventricles; hence it has a narrow spectrum of activity. It is not used clinically in veterinary medicine, but is used in human medicine for ventricular arrhythmias. It reportedly can cause defibrillation in cases of ventricular fibrillation in humans and has been investigated for similar effects in the dog (Rosalion et al., 1991). Because it causes the release of norepinephrine from adrenergic neurons, it may be associated with undesirable side effects.

Amiodarone is a powerful antiarrhythmic drug useful for both atrial and ventricular arrhythmias (Sicouri et al., 1997). In the normal canine heart, however, amiodarone causes negative inotropic effects (Ware et al., 1991). It also causes both α-blocking and nonselective β-blocking effects. Proarrhythmogenic effects are more likely in the presence of hypokalemia. Amiodarone is metabolized to an active metabolite in dogs. Amiodarone, however, shows only moderate efficacy for the treatment of arrhythmias (supraventricular or ventricular) in dogs and cats (Muir, 1991), although it was more effective than bretylium in preventing sustained ventricular tachycardia or fibrillation in a canine model of reperfusion arrhythmia (Rosalion et al., 1991). The drug presently is used in Europe and is under investigation in the United States.

Class IV Antiarrhythmic Drugs

Calcium channel blockers that are particularly effective in the vasculature are discussed with the vasodilator drugs. Diltiazem and verapamil have been used for both dogs and cats for their effects on heart rate. Both drugs are also, however, characterized by negative inotropic effects, with verapamil being a more effective but less safe negative inotrope.

Because calcium entry into myocardial cells is regulated primarily by slow channels, the CCBs also affect the heart. Specialized tissues capable of automaticity and atrioventricular conduction tissues are particularly affected by CCBs. The differences in pharmacologic effects induced by these drugs often result from their effect on the ability of the slow calcium channel to recover from inhibition (Robertson and Robertson, 1995). Calcium channel blockers that do not alter the rate of recovery will have little effect on conducting tissues. Drugs that do delay recovery of the channels can also delay conduction. For example, verapamil and diltiazem decrease the rate of recovery of calcium channels and thus not only decrease the magnitude of the cardiac action potential but also slow conduction through the atrioventricular node. The faster that atrioventricular nodal stimulation occurs, the more effective the atrioventricular nodal blockade is. Both drugs are useful for supraventricular arrhythmias. Because of their effect on slow calcium channels, they also decrease contractility.

In contrast, neither nifedipine nor amlodipine alters the rate of recovery, and as such they are minimally useful in the treatment of supraventricular arrhythmias (Robertson and Robertson, 1995). In contrast, verapamil has been shown to be useful in the treatment of ventricular tachycardias experimentally induced in dogs (De Micheli et al., 1997). It also appears to provide cardioprotective effects in dogs with acute Chagas disease, which is characterized by destruction of sympathetic nerve terminals and alterations of β-receptor density (Chen et al., 1996). A proposed mechanism is increased β-adrenergic adenylyl cyclase activity.

Diltiazem

Diltiazem (see Fig. 30–6) is the most commonly used calcium channel antagonist in veterinary medicine in part because it has been studied in both dogs and cats. It exerts its greatest effects in the sinoatrial and atrioventricular nodes, tissues in which slow Ca^{2+} influx is largely responsible for phase 0 depolarization. Diltiazem slows sinus rate and atrioventricular conduction. The ventricular rate is reduced in patients with atrial fibrillation or flutter, but primary ventricular arrhythmias are generally unresponsive to diltiazem. Myocardial oxygen demand decreases in response to the effects of diltiazem. Cardiac side effects include hypotension, bradycardia, and various degrees of heart block. In human patients, a therapeutic range of 50 to 300 ng/mL has been identified and can be used as a target for clinical response in animals.

Diltiazem is metabolized by acetylation, which is deficient in the dog but not in the cat. In an attempt to identify a product that allows convenient (once to twice daily) dosing intervals, the dispositions of several diltiazem products have been studied in cats. Comparison of IV, standard, and slow-release (CD) diltiazem preparations reveals a half-life of 120 minutes for the IV and PO preparations but 460 minutes for the CD preparation. The bioavailabilities of the PO preparations are 71% (standard) and 36% (CD). The higher bioavailability of the standard preparation for cats than for humans (30%) may reflect less first-pass metabolism because cats are efficient acetylators. Peak plasma concentrations for the standard preparation occurred at 45 minutes; peak steady-state concentrations of CD should occur at 2 days. Diltiazem is approximately 55% to 65% bound to serum proteins in cats. Maximum prolongation of the PR interval is less than 20% for either preparation, occurring at approximately 18 hours, when plasma diltiazem concentrations are between 50 and 100 ng/mL. The pharmacodynamic effects have not been studied in cats with hypertrophic cardiomyopathy. Based on these data, the standard diltiazem product is administered at 1 mg/kg every 8 hours, but the CD product (prepared in gelatin as either 60-mg or 90-mg capsules) can be administered at 10 mg/kg every 24 hours. More recently, Dilacor XR, another sustained-delivery diltiazem product, has been recommended. The product comes as a capsule containing four 60-mg pellets. One half of one of the pellets can be given once to twice daily.

Diltiazem has been studied in dogs (Maskasame et al., 1992; Nakamura et al., 1987). The PR interval is prolonged approximately 20% at plasma concentrations of 60 ng/mL. In dogs suffering from atrial fibrillation or CHF, diltiazem (0.5 to 1 mg/kg every 8 hours) can be used for its negative chronotropic effects to reduce heart rate in the presence of sustained supraventricular arrhythmias. Diltiazem can be used either alone or in combination with digoxin. Because of its negative inotropic effects, however, it must be used cautiously in patients with myocardial failure, and digitalization may be indicated before diltiazem therapy is begun. The drug can be used IV (0.2 to 0.4 mg/kg, followed by infusion of 4 to 8 μg/kg per minute), although extreme caution is recommended.

Verapamil

Verapamil is similar to diltiazem in its actions. It undergoes first-pass metabolism after PO administration. Although it is available in both IV and PO administration, caution is recommended with IV use. It has been studied for the treatment of acute supraventricular tachycardia in the dog at a dose of 0.05 to 0.15 mg/kg up to 0.2 to 5 mg/kg (Muir, 1991; Sisson and Thomas, 1995). Supraventricular arrhythmias that do not respond to Class IA drugs often respond to oral verapamil therapy (Muir, 1991). Among the CCBs used in small animals, verapamil is associated with the greatest negative inotropic effects and as such should be used cautiously in animals with ventricular myocardial dysfunction.

Miscellaneous Antiarrhythmic Drugs

Digoxin, a cardiac glycoside traditionally recognized to be a positive inotrope used to improve cardiac muscle contractility in the failing heart, is also a negative chronotrope due to both its direct (inhibition of Na^+,K^+-ATPase pump) and indirect (cholinergic-like) effects. In fact, its most common use in the treatment of canine CHF is probably as a negative chronotrope rather than a positive inotrope. Atropine also should be considered an antiarrhythmic by virtue of its blockade of vagally mediated cardiac slowing in some bradyarrhythmias. It is useful, however, only for short-term management. Longer acting orally administered anticholinergics (e.g., propantheline) are indicated only rarely for bradyarrhythmias, with pacemaker placement being the preferred treatment.

POSITIVE INOTROPES

A positive inotrope increases and a negative chronotrope decreases myocardial contractility. Although intuitively the use of a drug that increases cardiac contractility is reasonable in the patient with a failing myocardium, proof of clinical efficacy of positive inotropes is lacking, and their use is accompanied by controversy (Knight, 1991).

Positive inotropes can theoretically act by several mechanisms, most of which increase the quantity of calcium available for binding, which, in turn, augments contractile protein interaction in the myocardial cell (see Fig. 30–1). This can be accomplished several ways: increasing cAMP production by stimulating adenylate cyclase; decreasing cAMP degradation by inhibiting PDEs; altering the Na^+,Ca^{2+}-ATPase exchange pump; and, finally, directly stimulating the proteins in the cell membrane that control calcium channels (see Fig. 30–1).

Digitalis and Other Cardiac Glycosides

Digitalis has been used as a cardiac drug since at least the early 1200s (Snyder and Atkins, 1992; Kelly and Smith, 1995; Adams, 1995b). The therapeutic margin of the cardiac glycosides is narrow, but they have not been replaced with alternative safer drugs because none has yet been identified. The clinical efficacy of the cardiac glycosides probably reflects their actions as negative chronotropes as well as positive inotropes. Digitalis is used to increase the adequacy of circulation in patients with CHF and to slow the ventricular rate in the presence of supraventricular tachycardia (e.g., atrial fibrillation and flutter). It is likely that the major benefit of these drugs in most patients results from the latter effect.

Structure-Activity Relationship and Mechanism of Action

The source of digitalis is the dried leaf of the foxglove plant *(Digitalis purpurea)*. The active component of cardiac glycosides is an aglycone, which is released from attached sugars by hydrolysis (see Fig. 30–6) (Adams, 1995b; Kelly and Smith, 1995). The most probable mechanism of action for digitalis's inotropic effect is inhibition of the membrane-bound Na^+,K^+-activated adenosine triphosphate (Na^+,K^+-ATPase) "pump" (Fig. 30–9; see Fig. 30–1). The enzymatic activity is impaired, and the active transport, or exchange of these two ions, is impaired. As a result, there is a gradual increase in intracellular sodium. The cardiac fibers (both cell membrane and sarcoplasmic membrane) possess a second ATPase pump that exchanges Na^+ for Ca^{2+}. When the Na^+,K^+ pump is inhibited and Na^+ subsequently increases in the cell, the exchange of Na^+ for Ca^{2+} is augmented, and calcium influx is increased. The increased intracellular calcium, even though small, in turn leads to markedly increased release of Ca^{2+} from the sarcoplasmic reticulum during systole (see Fig. 30–1 and 30–2). Myocardial contractility improves, resulting in an increase in left ventricular function in both the normal and failing myocardium (Kelly and Smith, 1995). In people, the increase in contractility occurs at serum levels of 1.4 ng/mL (Kelly and Smith 1995).

The ability of digoxin to decrease neurohumoral activation associated with heart failure also has been examined (Kelly and Smith, 1995). Inhibition of the sodium pump in neuronal cells, particularly in the baroreceptor, results in stimulation of parasympathetic and inhibition of sympathetic nerves. Digoxin appears to directly alter carotid baroreflex responsiveness to changes in carotid sinus pressure in animals with heart failure. Other indirect effects of digitalis also result from increased efferent vagal (cholinergic) effects. These effects are more pronounced on atrial fibers and specialized cardiac pacemaker and conduction fibers. Digoxin decreases automaticity, increases the diastolic resting membrane potential, increases the effective refractory period, and decreases conduction velocity, particularly in atrial and atrioventricular nodal tissues. Digitalis also decreases the number of atrial impulses that are transmitted to the ventricles through the atrioventricular node during atrial fibrillation or flutter. These effects reflect both an increased vagal tone and a decreased sympathetic nervous system activity (Kelly and Smith, 1995), causing slowing of the heart rate, particularly in patients with a rapid heart rate.

These effects occur at serum digoxin concentrations of 1.3 ng/mL (Kelly and Smith, 1995), thus at concentrations that are not toxic, and probably at concentrations less than those associated with peak contractility (Kelly and Smith, 1995). As serum digoxin concentrations increase, however, sinus bradycardia or arrest, prolongation of atrioventricular conduction, heart block, or increased sympathetic nervous activity with increased automaticity may occur. The negative chronotropic effects of digitalis can be ameliorated with atropine. Paradoxically, in the presence of digoxin, atria are sensitive to acetylcholine, atrial conduction is

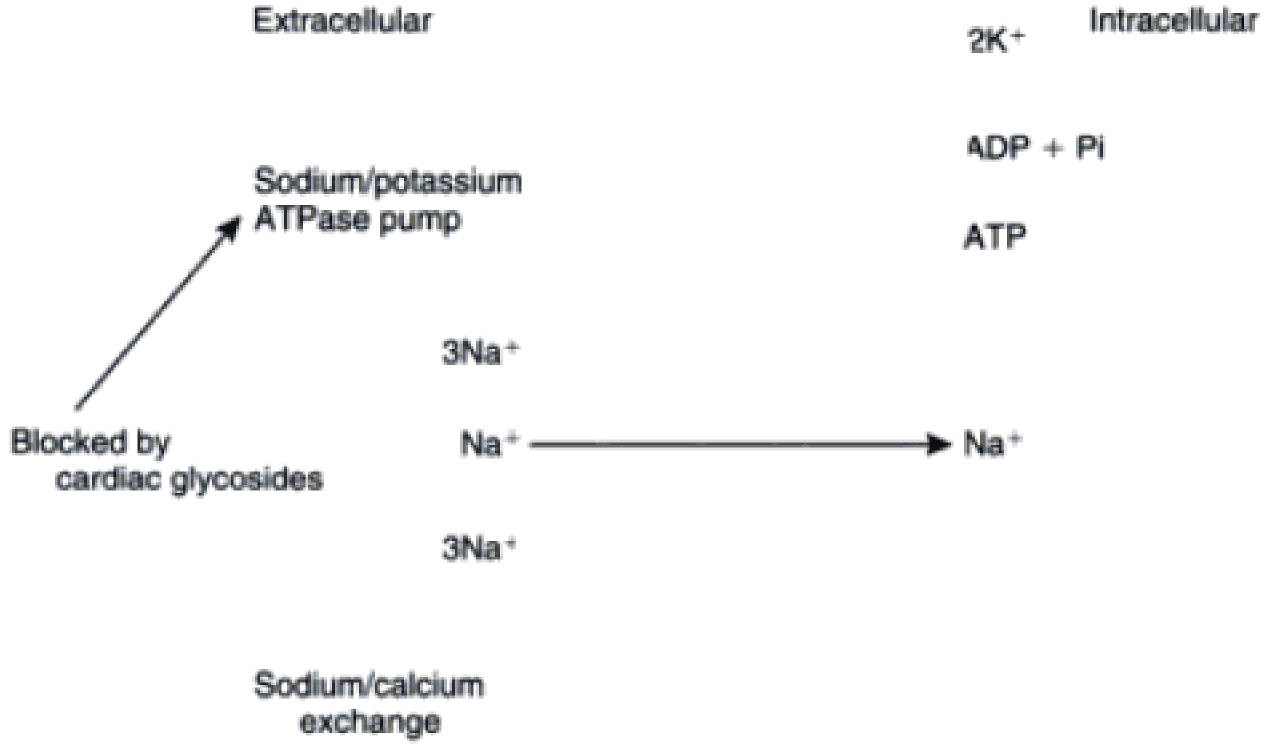

Figure 30–9. Mechanism of action of digoxin. Blockade of the sodium/potassium ATPase pump causes an increase in intracellular sodium, initiating the sodium/calcium ATPase pump. Increased intracellular calcium is sufficient to stimulate intracellular release of calcium, increasing contractility. Myocardial arrhythmias caused by digoxin reflect, in part, disruption in cell membrane fluxes of sodium, potassium, and calcium. ADP = adenosine diphosphate; ATP = adenosine triphosphate.

enhanced, and, in the diseased heart, the risk of atrial tachycardias (e.g., atrial fibrillation) is increased. Increased intracellular calcium contributes to the arrhythmogenicity of digoxin (Kelly and Smith, 1995). Digitalis has only minor indirect effects in ventricular tissue.

The effects of cardiac glycosides on myocardial oxygen demand depend on the net effect on cardiac function. Mechanistically, energy utilization shifts from one ATPase pump to another, which might minimize the increase in oxygen needs. In normal hearts, however, oxygen demand increases proportionately with increased contraction (Adams, 1995b). If ventricular volume decreases and systolic wall stress declines, however, as would be expected in an animal with myocardial failure, improved cardiac function and subsequent decreased fiber length will compensate for the increased oxygen demand caused by improved contractility (Knight, 1991; Adams, 1995b).

Cardiac glycosides can cause peripheral arterial and venous vasoconstriction, but these effects are more likely in the normal animal (Kelly and Smith, 1995). Pulmonary vasoconstriction is induced by all except digoxin. Effects in the vasculature are more common after IV administration and occur in less than 15 minutes; indeed, with PO administration, vasodilation predominates. Thus, oral digitalization with digoxin will minimize the risk of adverse effects caused by cardiac glycoside-induced vasoconstriction (Knight, 1991).

Clinical Pharmacology

Digoxin and digitoxin are the two most widely used preparations. The dispositions of both drugs have been studied in dogs (Breznock, 1973; De Rick et al., 1978; Button et al., 1980a,b). The disposition of the cardiac glycoside is quite variable among animals and preparations. Plasma drug concentrations accordingly are variable. Oral absorption of digoxin is variable and depends on the preparation, varying from 40% to 90%. Absorption of the alcohol (i.e., elixir) form is best. Up to 90% of the dose is absorbed, with peak concentrations occurring in 45 to 60 minutes (Adams, 1995b). Variation in bioavailability of tablets results from differences in dissolution between products. Absorption is retarded by food. The absorption of digitoxin is much more complete because it is more lipid soluble. Both drugs are distributed slowly, in part because of a large volume of distribution. The volume of distribution includes most body tissues. The drug is concentrated in cardiac tissues. Only 25% of digoxin is protein bound, whereas most of digitoxin is (90%) protein bound.

Doses of digitoxin generally must be higher than those of digoxin in part because it is highly protein bound. Because it is minimally bound, digoxin should have faster effects. Digoxin is primarily eliminated unchanged in the kidneys. Its reported half-life is quite variable, ranging from 21 to 60 hours (Adams, 1995b), with a working average of 1.7 days. Even in the same animal, digoxin half-life can vary (e.g., 154 to 46 hours in one study) (Adams, 1995b). Elimination half-life thus is strongly influenced by renal function, and greater variability can be expected in animals in which renal function changes with the progression of cardiac disease and its response to therapy. For example, we have calculated elimination half-life for digoxin as short as 9 hours in animals concurrently receiving an ACE inhibitor and diuretic therapy and longer than 48 hours in animals with presumed renal dysfunction. It is this variability in half-life that leads to my recommendation that both peak and trough concentrations be collected when monitoring digoxin (see Chapter 4).

Digitoxin is metabolized by the liver (one of the products is digoxin), and its metabolism is affected by factors that alter the microsomal system, but not by hepatic disease. Despite binding to serum proteins and hepatic metabolism, its half life of 8 to 12 hours in dogs is shorter than that of digoxin, necessitating more frequent dosing. Digitoxin undergoes a small enterohepatic cycle. Variation in disposition among animals coupled with a narrow therapeutic range makes digoxin toxicity very possible.

Preparations and Dosing Information

Digoxin is available for IV or PO administration. Intravenous administration results in pharmacologic effects in 5 to 30 minutes, with a maximal effect in 2 hours. It should not be given IM because it causes pain and necrosis. Oral administration results in pharmacologic effects in 1 to 2 hours, although peak effects may not occur until later. Digoxin elixir is more bioavailable, and doses may need to be decreased by 15%. If deemed necessary, oral digitalization is best accomplished with digoxin tablets. In the absence of a loading dose, steady-state concentrations can be achieved within 48 hours of oral dosing. A prudent IV loading dose is administration of the oral daily maintenance dose over a 12-hour period (Knight, 1991). Doses should be calculated on lean body weight; toxicosis is likely to be minimized if dosing is based on body surface area (0.44 mg/m^2). Daily doses should be divided if warranted based on drug elimination half-life (as calculated from therapeutic drug monitoring) to minimize fluctuation in plasma drug concentrations.

Drug Interactions

The concurrent administration of quinidine increases plasma concentrations of digoxin, probably due to displacement from tissue binding sites, although this mechanism may be controversial (Doering, 1979; Colvin et al., 1990). Verapamil also increases concentrations of digoxin (Knight, 1991). Interactions between digitalis and diuretics stem primarily from the effects on potassium (hypokalemia). Diuretics do not seem to alter the disposition of digoxin (Ravis et al., 1987). Phenobarbital has been reported to increase (rather than decrease) digoxin concentrations; the clinical relevancy of this report is not clear (Pedersoli et al., 1980; Ravis et al., 1987). Administration of β-adrenergic agonists increases the likelihood of arrhythmias. Amphotericin B may also cause hypokalemia and thus potentiate digitalis intoxication.

Clinical Efficacy

Inotropic response to digoxin is greatest in the initially depressed state of the failing heart. Stroke volume increases as ventricular emptying improves, with a reduction in end-diastolic volume (Knight, 1991). This positive effect is less

hypercalcemia, hypomagnesemia, hypothyroidism, acid-base imbalances, and abnormal renal function (Kelly and Smith, 1995). Combination therapy with other drugs also predisposes the patient. Selected digoxin preparations also are more likely to cause toxicity because of differences in absorption. The cat is more sensitive to digoxin than the dog.

The most frequent cause of digoxin toxicity is probably overdosing. The potential for toxicity is increased with hypokalemia because binding to the Na^+-ATPase pump is facilitated. This may occur, for example, if the patient is also receiving diuretic therapy that causes potassium loss (furosemide, thiazides, and other "nonsparing" diuretics). Digitalis toxicity can be diagnosed and the risk minimized by plasma drug concentration monitoring. Therapeutic concentrations of digitoxin are 1.4 to 2.6 ng/mL, with concentrations greater than 3.4 ng/mL considered toxic (Adams, 1995b). The recommended range for digoxin is likely to vary with the laboratory but generally is 1.5 to 2.5 ng/mL. The targeted concentration for either cardiac glycoside in the individual animal should be based on clinical signs, including response to therapy. The risk of toxicosis is greater if concentrations exceed 2.0 to 2.5 ng/mL (De Rick et al., 1978). Because the elimination half-life of digoxin can be so variable in dogs with CHF (our experiences), both peak and trough concentrations (at 2 and 11.5 hours after PO administration) may be needed in order to design an appropriate dosing regimen. If only a single sample is possible, the time of selection collection depends on the intent of monitoring. If toxicity is of concern, a peak sample should be collected at 1 to 2 hours after administration; if efficacy is of concern, then a trough sample should be collected. Neither situation will, however, offer guidance of drug concentrations throughout the dosing interval.

The treatment of cardiac glycoside intoxication includes (1) discontinuation of digitalis therapy for at least one drug elimination half-life; (2) discontinuation of potassium-depleting diuretics; (3) administration of phenytoin, which blocks atrioventricular nodal effects of digitalis (bradyarrhythmias), lidocaine (for ventricular arrhythmias) (Akiyama and Hashimoto, 1990) (1–3 mg/kg IV), and oral potassium supplementation (e.g., potassium chloride), but only if hypokalemia exists (Adams, 1995b). Atropine may be useful to treat sinus bradycardia and second-degree or third-degree heart block induced by cholinergic augmentation. Procainamide also has been shown experimentally to be useful for treatment of digoxin-induced ventricular arrhythmias in the canine heart when plasma drug concentrations approximate 8 to 12 ng/mL (Endou et al., 1987; Hashimoto et al., 1985). Cholestyramine can be used as a binding agent to decrease absorption from the gastrointestinal tract (including drug undergoing enterohepatic circulation).

Purified antibody fractions (Fab) to digoxin have proved to be an effective antidote to digoxin toxicity in people. Although they have been successfully used by the author to treat an accidental overdose of digoxin, their cost is likely to be prohibitive. For people, a full neutralizing dose costs $2000 to $3000. Dosing is complicated, being based on the total amount of digoxin in the body. This can be estimated based on the amount ingested and the average bioavailability or on serum digoxin concentrations and the average volume of distribution (Kelly and Smith, 1995). Toxicity can recur once the Fab has been eliminated 1 to 2 days after therapy, particularly in patients with impaired renal function.

Clinical Use

Clinical uses of digitalis include restoration of adequate circulation in patients with CHF and reduction of the ventricular rate as a treatment of atrial fibrillation or flutter. Both syndromes require long-term treatment. If there is no urgency in treatment, the drug can be administered orally. Maximal effect is achieved in four half-lives.

Digoxin is the cardiac glycoside drug of choice except for the patient with renal disease; digitoxin should then be administered. Calculation of digoxin doses should be based on lean body weight, and dosages should be reduced in the obese patient in the presence of ascites. Electrolyte disorders should be corrected before dosage.

Phosphodiesterase Inhibitors

Phosphodiesterase inhibitors prevent the breakdown of cAMP and therefore increase intracellular cAMP concentrations. The result is an increase in myocardial contractility.

Methylxanthine Derivatives

Methylxanthine derivatives have been classified as PDE inhibitors, but the mechanism of action is controversial. Their mechanism of action may actually be due to altered calcium fluxes or other mechanisms. Of the methylxanthines, theophylline is the most cardiopotent. The positive inotropic effects of these drugs are complex because they have a variety of pharmacologic actions. In addition to their cardiac effects, these drug have significant CNS, renal, and smooth muscle effects. Thus, their use for cardiac disease is limited.

Fatal toxicities can occur and usually do occur during chronic PO or rapid IV administration, probably due to cardiac effects. Tachycardia and CNS signs (restlessness, hyperexcitability, sensory disturbances) can be correlated with increased plasma concentrations. Plasma monitoring may be used to control toxicity. Local gastrointestinal irritation and nausea, vomiting, and diarrhea may occur with PO administration. These can be avoided by administration of the drugs with food.

Therapeutic uses for the methylxanthines in cardiac disease are limited. In veterinary medicine, theophylline has been used to treat CHF. Currently, these drugs should only be used in cardiac patients with respiratory disease.

Bipyridines

Bipyridines are "nonglycosidic, noncatecholamine" positive inotropes that act similarly to catecholamines in the heart. Unlike catecholamines, myocardial oxygen consumption is not dramatically increased. Peripheral vasodilation is another major therapeutic benefit of these drugs. Amrinone was the first of this class of drugs to be used therapeutically, but it is associated with too many side effects. In contrast, milrinone is more potent yet characterized by a toxic to therapeutic ratio of 100 in normal dogs, despite being 20 to 30 times as potent as amrinone.

The mechanism of action of these drugs is probably inhibition of PDE and increased intracellular cAMP concentrations. These effects appear to be induced without a dramatic rise in myocardial oxygen consumption. Differences in potency and toxicity when compared with theophylline may reflect selective PDE isoenzyme inhibition for each group of drugs. The bipyridines inhibit PDE III only, whereas theophylline may be nonselective inhibitors of PDE. Pilot studies indicate an elimination half-life of about 1.4 hours for milrinone in dogs, although this is likely to be quite variable (Kittleson, 1991). Oral bioavailability approximates 92%.

Intravenous or oral administration of milrinone results in marked positive inotropic effects in patients with congestive heart failure. Effects are dose dependent. Contractility increases up to 100% at plasma concentrations of 200 mm/L after infusion of 10 g/kg per minute in anesthetized dogs versus only 60% in patients receiving digitalis. An oral dose of 1 mg/kg increases contractility 90% and decrease blood pressure by 10%. Heart rate also, however, increases 40%. As with drug disposition, individual animal response to milrinone appears to be quite variable (Kittleson, 1991). As with the cardiac glycosides, animals with very poor myocardial function may not be able to respond to the bipyridines. In clinical trials in dogs with CHF, approximately 80% of animals reportedly respond (Keister et al., 1990). Survival data were not reported for dogs. Milrinone does not appear to be as effective a positive inotrope for people as it is for dogs.

Milrinone appears to be substantially safer than digoxin when given at an oral dose of 0.5 to 1 mg/kg twice daily. In people with myocardial failure, myocardial oxygen consumption does not increase and may decrease after treatment with milrinone. Exacerbations of arrhythmics may occur in some animals. Ruptured chordae tendineae (4%) and sudden death (13%) were other complications reported in clinical trials with dogs with CHF. The current status of milrinone is not clear, but apparently it is still undergoing consideration for approval for dogs.

β-*Adrenergic Agonists*

The β-adrenergic agonists include the catecholamines (norepinephrine, epinephrine, isoproterenol, dopamine, and dobutamine). The mechanism of action of the positive inotropic effects of these drugs is stimulation of adenyl cyclase and increased cAMP (see Fig. 30–1). These drugs are the most potent myocardial stimulants, each causing increased contractility. In addition, depending on the drug, potent peripheral vasomotor responses tend to limit their use clinically as positive inotropes.

Dopamine

Dopamine is an endogenous catecholamine (norepinephrine) precursor with selective β_1 activity that is widely used as a cardiac stimulant. Because it stimulates the release of norepinephrine, however, it has α-receptor–, β_2-receptor–, and dopaminergic receptor–mediated actions as well. Its inotropic effects are due to β_1-receptor stimulation in the heart. At low doses (4 μg/kg per minute), it increases stroke volume and cardiac output and stimulates renal dopaminergic receptors, causing increased renal blood flow and diuresis. This is useful during situations of systemic vasoconstriction (e.g., shock) during which it is important to maintain renal blood flow. At high doses, however, it causes α stimulation and vasoconstriction. This may potentially reduce renal blood flow. Dopamine appears to increase systolic pressure without significantly affecting diastolic pressure.

Dopamine is not effectively absorbed orally. It is rapidly metabolized by the body by monoamine oxidase and catecholamine-*O*-methyltransferase (COMT) and has a half-life of less than 2 minutes. Dopamine is most commonly marketed as a solution that is further diluted with saline or dextrose. The drug is administered intravenously. Because the pharmacologic effects of dopamine are short lived, it is usually administered by constant infusion, and rate of administration can be used to control the intensity of effects.

Cardiac arrhythmias may occur due to β-adrenergic activity. Dopamine should not be used in the hypovolemic patient (due to potential for enhanced vasoconstriction?). Tissue sloughing may occur in the event of perivascular leakage. Indications include cardiogenic, or endotoxic, shock and oliguria.

Dobutamine

Dobutamine is a synthetic drug that is similar to dopamine but has a large bulky molecule associated with it. Its mechanism of action is similar to that of dopamine, but it has fewer non-β_1 effects. Dobutamine is a more effective inotrope than dopamine and is not associated with increased cardiac rates at lower doses. Dobutamine appears to increase cardiac contractility with less cardiac oxygen consumption than other catecholamines. Dobutamine does not dilate the renal vascular bed as does dopamine, although in a canine model of endotoxic shock it increased urine output and mesenteric blood flow at 5 and 10 μg/kg per minute (DeBacker et al., 1996). Because of its greater selective effect on contractility as opposed to increasing heart rate, it is preferred to dopamine as a positive inotrope for treatment of CHF that is severe and eminently life threatening. Its arrhythmogenicity is less than that of epinephrine and is not likely to occur (in normal dogs or dogs with ventricular ectopic beats) until therapeutic doses have been exceeded.

Dobutamine is not effective orally and has a plasma half-life of approximately 2 minutes due to metabolism by COMT. It is therefore usually administered by constant intravenous infusion. The drug is metabolized in the liver to inactive glucuronide conjugates. Like dopamine, dobutamine is prepared as a solution to be diluted with dextrose. It is stable only for 6 hours after dilution. The major indication for dobutamine is short-term therapy for refractory CHF. It is the preferred drug (e.g., compared with digoxin) because its short half-life reduces the potential for toxicity and the inotropic effects of dobutamine are greater. Treatment beyond 48 hours is discouraged, in part because of the development of tolerance. In people, however, a residual effect occurs for up to several months. Dobutamine and volume replacement are indicated for treatment of hemorrhagic shock (Luo et al., 1997). Likewise, in dogs with septic shock, dobutamine (5 to 10 μg/kg per minute) increases mesenteric blood flow and urine output when administered in conjunction with fluid therapy (DeBacker et al., 1996).

The dose generally recommended is 2.5 to 10 μg/kg per minute. Improvement should occur within 30 minutes, and doses can be increased 1 to 2 μg/kg per minute every 30 minutes until side effect preclude further dose increases. The most common side effect is ventricular arrhythmias, which are less likely to occur if doses of 15 μg/kg per minute are not exceeded. Animals with very severe CHF and very poor myocardial function may not be able to respond to dobutamine because of little contractile reserve.

Epinephrine

Epinephrine is one of the most potent vasopressor drugs known. It causes an immediate rise in blood pressure due to (1) direct myocardial stimulation and a positive inotropic effect, (2) an increased heart rate or positive chronotropic effect, and (3) vasoconstriction in many vascular beds. As with the other catecholamines, its cardiac effects are due to direct interaction with β_1-receptors and cells of the pacemaker and conducting tissues. Cardiac systole is shorter and more powerful. Because the formation of cAMP requires ATP, however, epinephrine causes the greatest increase in the rate of energy usage and myocardial oxygen demand. This increase in oxygen need may be detrimental to the failing heart. Increased work and myocardial oxygen consumption result in *reduced* cardiac efficiency.

Epinephrine is rapidly metabolized in the gastrointestinal tract and does not reach therapeutic plasma concentrations after PO administration. Absorption is more rapid after IM versus subcutaneous (SC) administration because of local vasoconstriction. Epinephrine is rapidly metabolized by the body. The liver plays an important but not essential role in the metabolism of epinephrine. Two enzymes catalyze its degradation: COMT and monoamine oxidase.

Epinephrine is available in several forms of solution that can be used for IV, inhalation, and nasal administration. Because of the decreased efficiency of cardiac work, epinephrine is not used simply as a positive inotropic agent. Ventricular arrhythmias can be expected. In addition, CNS signs may occur. The primary indication for epinephrine in treatment of cardiac disease is acute cardiac life support (see "crash cart" drugs).

Isoproterenol

Isoproterenol is a nonspecific β-agonist that, like epinephrine, increases myocardial oxygen demand. Tachycardia and the potential for other arrhythmias tends to exclude its use for the cardiac patient.

Miscellaneous Agents

Miscellaneous inotropic agents include calcium when given as a slow IV injection or infusion. Care must be taken with the administration of calcium because it can cause cardiac rigor and standstill at high doses. The gluconate form is preferred to calcium chloride. Glucagon is also a positive inotropic agent.

Coenzyme Q, also called ubiquinone, is a natural fat-soluble compound similar to vitamin K in structure and ubiquitous in plants and animals. It acts as an antioxidant to protect cell membranes from free radical activity. The use of the compound is being considered in patients with severe congestive heart failure (150 to 225 mg/day), particularly for those whose endogenous concentrations fall below 2 μg/mL. The effects of Coenzyme Q on myocardial cells is controversial. In cultured myocardial cells, Coenzyme Q stimulates beating activity, probably by stimulating the formation of mitochondrial ATP (Kishi et al., 1993). In humans undergoing valve replacement, Coenzyme Q appeared to scavenge hydroxyl but not superoxide anions (Zhou et al., 1999). Singh and coworkers (1999) demonstrated a protective effect of Coenzyme Q in patients receiving the compound within 3 days following acute myocardial infarction, However, a lack of effect on ventricular function was reported in patients with congestive heart failure (Langsjoen, 2000). Coenzyme Q may block apoptosis (Kagan, 1999). Foods highest in Coenzyme Q include beef, spinach, sardines, albacore tuna, and peanuts. Coenzyme Q is available as a dietary supplement, generally in capsules ranging in size from 10 to 60 mg.

Nutritional intervention with essential nutrients, including L-arginine and L-carnitine, also has been recommended as effective adjunctive therapy for prevention and control of cardiovascular disease (Kendler, 1999).

NEGATIVE INOTROPES

The negative inotropes most commonly used in clinical practice are those that block β-receptors (propranolol, which is nonselective, or atenolol, which selectively blocks β_1-receptors) or CCBs (diltiazem). By virtue of their mechanisms of action, drugs in either of these categories also tend to act as negative chronotropes; often this action is desirable. Both groups of drugs have been previously discussed as antiarrhythmics. These drugs are further discussed under treatment of hypertrophic cardiomyopathy.

The primary indication for the use of negative chronotropes in veterinary medicine is feline hypertrophic cardiomyopathy, a cardiac disease characterized by a thickened cardiac muscle, poor distensibility and compliance, and thus poor cardiac filling, and, depending on the degree of ventricular hypertrophy, obstruction to cardiac outflow. Atrial fibrillation is not uncommon in this syndrome and generally causes a tachycardia that worsens this syndrome. Thus the negative chronotropic effects of these drugs are of benefit in cats suffering from hypertrophic cardiomegaly.

TREATMENT OF SPECIFIC VASCULAR DISORDERS

Acquired Valvular Diseases

Chronic Mitral Valve Insufficiency

Pathophysiology

Chronic mitral valve insufficiency (CMVI) results from endocardiosis of the mitral valve and is the most common

and pulmonary capillary pressure. Afterload reduction, diuretics, and positive inotropes are indicated in that order, depending on the severity of clinical signs and the presence of myocardial dysfunction. The most appropriate afterload reducer again may be based on the presence or absence of myocardial failure and compensatory mechanisms. Diuretics initially may play a more active role in the presence of pulmonary edema, but a decreasing need may be evident after several weeks of therapy. In the case of acute cardiogenic pulmonary edema (i.e., that which is life threatening), morphine may be helpful. Its central effects may reduce stress and anxiety and the negative sequelae of vascular responses to stress. Respirations may deepen, slow, and result in improved ventilation. In addition, ventilation may result in pooling of blood in the splanchnic vasculature, reducing preload. Care should be taken to not overdose with morphine (0.1 to 0.22 mg/kg SC; repeat as necessary).

The enlargement of the left atrium may result in the development of supraventricular tachycardias in animals with CVMI. Ventricular rates greater than 180 beats per minute (bpm) are likely to reduce cardiac output. An added goal of drug therapy for such patients is reduction of heart rate to 150 to 160 bpm or less. Digoxin is the preferred antiarrhythmic drug, with the addition of either diltiazem or selective β_1-blockers or metoprolol. The potential benefits of β-blockers on the diseased myocardium (see discussion under antiarrhythmics) warrants strong consideration of their use (White, 1998). Cardiac decompensation may occur in some patients if the heart rate drops below 150 bpm; animals whose heart rate depends on sympathetic activity may be particularly sensitive to β-blockade (O'Grady, 1995).

Right-sided heart failure is described as a common complication of CMVI (O'Grady, 1995). Because the right ventricular wall is thinner than the left ventricular wall, it is more compliant and thus better able to adjust to the increased volume associated with tricuspid insufficiency. It does not, however, adjust as well to increases in pulmonary pressure. Right ventricular stroke volume can markedly decrease in the face of very small increases in pulmonary pressure, resulting in decreased delivery to the left ventricle and decreased cardiac output. The use of systemic vasodilators in the presence of pulmonary hypertension may further decrease cardiac output. Unfortunately, pulmonary hypertension is not conducive to selective pharmacologic management. Among the current vasodilators used, hydralazine appears to be the most likely to induce preferential dilation of the pulmonary arterial tree compared with the systemic vasculature. Hydralazine decreases pulmonary vascular resistance in both normal lungs and in lungs with experimentally induced embolization (Lupi-Herrera et al., 1992). Because hypoxia can worsen pulmonary arterial vasoconstriction, oxygen therapy is critical to the treatment of pulmonary hypertension associated with CVMI. Aggressive diuretic therapy is indicated to reduce pulmonary edema as well as pulmonary hypertension. Bronchodilator therapy may facilitate bronchiolar smooth muscle spasm, facilitating air movement. Theophylline has been associated with ventilation perfusion mismatching, so oxygenation is important. This adversity has not, however, been addressed in the presence of pulmonary hypertension. β_2-Adrenergics may be an equally acceptable bronchodilator alternative to theophylline.

Ruptured chordae tendineae has been described as possibly the most frequently encountered complication of CVMI (O'Grady, 1995). The sequelae of rupture appear more dependent on which (i.e., first, second, or third order) rather than how many rupture. The negative sequelae generally reflect the left atrium's inability to accommodate to the rapid increase in left atrial pressure. Patients may present in severe respiratory distress as pulmonary capillary pressure and pulmonary (interstitial and alveolar) edema develop. Right-sided heart failure (manifested as pleural effusion or ascites) also may be present. Treatment includes aggressive diuretic therapy (furosemide at 8 mg/kg IV every 6 hours). Rapidly acting positive inotropes (dobutamine or dopamine) may facilitate emptying of the left ventricle and thus decrease the size of the mitral annulus. Afterload reducing agents appear to be of no benefit and may be deleterious if cardiac output decreases. Preload reducing agents are probably less beneficial with right-sided failure.

Tricuspid Valvular Insufficiency

Because a normally functioning left ventricle ensures forward movement of blood in the right ventricle, incompetency of the tricuspid valve generally does not lead to cardiac insufficiency unless accompanied by an underlying disease (e.g., pulmonary hypertension, heartworm diseases, CMVI). Identification of any underlying disorder leading to tricuspid valvular insufficiency is critical to successful management of cardiac insufficiency. Loop diuretics (furosemide) or aldosterone antagonists (spironolactone) (or a combination thereof) may be indicated for management of ascites. Digoxin may be helpful in the presence of myocardial failure, and antiarrhythmic drugs may be necessary to control tachycardia (O'Grady, 1995).

Diseases of the Myocardium

Dilated Cardiomyopathy

Pathology

The cause of dilated cardiomyopathy (DCM) in dogs is not known, although a number have been proposed (e.g., viral, nutritional, toxins, hereditary). Often secondary changes cannot be discerned from primary changes (i.e., which is cause and which is effect). Biochemical changes similar to those accompanying DCM in humans have been identified in dogs, including decreased myocardial carnitine or myoglobin concentration, decreased β-receptor–mediated adenyl cyclase (e.g., down regulation of receptors or decreased intracellular proteins), decreased intracellular regulatory proteins (e.g., light chains), or altered calcium release from the sarcoplasmic reticulum. Among these causes, decreased carnitine has received the most attention (Keene, 1991). Carnitine is responsible for the transport of fatty acids into mitochondria where they are subjected to β-oxidation; carnitine deficiency then might be characterized by altered energy metabolism and lipid accumulation in the myocardium. Clinical trials have, however, suggested

rhythmias can be treated with the addition of propranolol or a change to quinidine, tocainide, or mexiletine.

Atrial fibrillation is among the most common atrial arrhythmias associated with DCM. Digoxin is the antiarrhythmic drug of choice not only for its negative chronotropic effect (including atrioventricular nodal impulse suppression) but also for its positive inotropic effects (see below). Should digoxin fail to control the heart rate, a CCB (e.g., diltiazem) or a β-adrenergic blocking drug (propranolol, atenolol) is indicated. Either type of drug also can be used to treat persistent sinus tachycardias. Although no study has documented increased efficacy of one class of drugs over another for dogs, β-blockade apparently has improved survival for human patients with cardiac failure. The risk of sudden detrimental effects on myocardial function and cardiovascular effects in patients should, however, lead to caution when β-blockers are used for the patient with severe heart failure. Selected CCBs can have a similar effect; diltiazem may be the least likely to detrimentally impact cardiac function in patients with severe disease (Sisson and Thomas, 1995).

Digoxin is indicated as a positive inotrope in patients with DCM and clinical signs indicative of CHF. The positive inotropic effects can be marked in some dogs with DCM (Kittleson et al., 1985; Ferguson et al., 1989). Negative chronotropic effects likewise will benefit most patients (Hamlin, 1992). Both pharmacologic effects act to reduce activation of the RAA system (Sisson and Thomas, 1995; Ferguson et al., 1989). Studies in human patients with DCM have detailed the reduction of clinical manifestations, improved capacity for exercise, and slowed progression of disease induced by digoxin therapy (Sisson and Thomas, 1995). The use of PDE inhibitors in dogs with DCM has not been established. Both milrinone and amrinone are used short term by human patients with heart failure. The vasodilating properties of these positive inotropic drugs are beneficial. In dogs with DCM, the positive inotropic effects of milrinone improve hemodynamic function and clinical signs (Kittleson, 1985). Long-term use with milrinone has been limited by evidence of increased mortality in human patients (Sisson and Thomas, 1995). The absence of coronary arterial disease in dogs may, however, minimize the risk associated with the use of milrinone for long-term treatment of DCM. Despite its potential benefits, milrinone is not generally used to treat DCM. Several new PDE inhibitors (pimobendan, vesnarinone) are being studied. Because of their effects on myocardial oxygen demand, the use of β-adrenergic drugs as positive inotropes should be limited to life-threatening severe myocardial failure. Expense and down-regulation of β-receptors limit the use of these drugs to acute management. Dobutamine is the preferred drug; vasodilators should be used simultaneously.

ACE inhibitors are indicated for dogs with DCM and clinical signs of cardiac failure. In a clinical trial of 110 dogs in 15 locations throughout the United States, when enalapril was used in combination with other drugs indicated for treatment of DCM, the mean number of days until treatment failure increased from 56.6 (placebo) to 143 (enalapril) (Ettinger et al., 1998). Less clear is the indication in the absence of clinical signs. Both increased afterload and preload (sodium and water retention) may be contributing to the progression of disease without causing overt clinical signs of decompensation. The presence of an ACE inhibitor may reduce the necessary dose of other drugs used to control clinical signs (e.g., furosemide).

Diuretics are indicated for patients with signs of congestion. For severe pulmonary edema, therapy should be aggressive (IV, high doses). Oral therapy is indicated for control and long-term management. Dogs should be closely monitored for the advent of dehydration, excessive preload reduction, and subsequent decreases in cardiac output. Azotemia may develop. Although not common, hypokalemia may occur. In patients that are refractory (e.g., pleural effusion or ascites) to furosemide (particularly right-sided heart failure in which oral absorption may be reduced), parenteral rather than oral therapy may improve response. Alternatively, butemide is more orally bioavailable in people and may likewise be better absorbed in dogs (Sisson and Thomas, 1995). Alternative managements include the addition of a thiazide diuretic to furosemide therapy, a venodilator, or an ACE inhibitor.

The role of β-blockers for treatment of heart failure is currently being investigated (see discussion under antiarrhythmics) as a means of decreasing the progression of myocardial disease. Metoprolol and carvedilol are the most promising (Cleland, 1999).

Feline Dilated Cardiomyopathy

The recognition that DCM in cats was largely reversible with the administration of taurine has all but eliminated DCM in cats (Sisson, 1991; Pion et al., 1992). Most commercial feline diets now contain sufficient taurine to prevent the syndrome. A history of unconventional foods or homemade diets will help to easily identify the occasional cat with cardiac disease associated with taurine deficiency. The clinical presentation of DCM in cats is similar to that in dogs, although pleural effusions are more common. Systemic thromboembolism is another potential complication. Plasma taurine concentrations are often but not always low (<30 nM/mL). Systemic thromboembolism apparently can increase, and fasting can decrease, plasma taurine concentrations. Taurine supplementation largely reverses the clinical signs and ECG abnormalities associated with taurine deficiency. Most animals respond to taurine supplementation (250 to 300 mg/day PO) within 3 to 6 weeks of therapy. Mortality is highest, however, during the initial 2 to 3 weeks of therapy. Echocardiography is the preferred method for monitoring response to therapy because response times can markedly vary. Adjuvant therapy may be necessary until clinical response.

Diuretics (furosemide) can be used to manage pulmonary edema and pleural effusions; differences in dosing regimens for cats compared with dogs should be observed. Cats may appear to be dehydrated (based on skin turgor), but this is more likely to represent redistribution of fluids to the pleural cavity or lungs. Fluid may be necessary in the presence of azotemia associated with low-output failure and hypotension but should be administered only cautiously and slowly. Digoxin (0.0035 to 0.0055 mg PO every 12 to 24 hours) may be indicated until the response to taurine is evident. Emergency management of myocardial failure may require administration of dobutamine (2 to 5 μg/kg per minute); common side effects of dobutamine

with retinal detachment have a higher pressure than cats without detachment (Henik, 1997). Retinal arteries may be tortuous.

Systolic and diastolic pressures are, respectively, the upper and lower limits of the oscillations around mean arterial pressure. The mean arterial pressure is the arterial pressure over time and is defined as the diastolic pressure plus one third of the pulse pressure. Arterial blood pressure is the product of cardiac output (determined by stroke volume and heart rate) and total peripheral resistance. Total peripheral resistance is the sum of resistance in all vascular beds. It is also impacted by aortic impedance (resistance to flow) and diastolic arterial pressure, which in turn is determined by the sympathetic nervous system, the RAA and AVP systems, vascular (extracellular fluid) volume, and aldosterone or other volume active hormones (Henik, 1997).

Proper measurement of blood pressure is paramount to successful management of systemic hypertension. Measurements should be taken after an animal has had proper time to acclimate to its surroundings but under conditions of minimal stress (Henik, 1997). Among the indirect methods used to measure systemic blood pressure in cats, the Doppler and photoplethysmographic methods are probably preferred (Sisson and Thomas, 1995). Care must be taken to follow proper techniques with the appropriate equipment when blood pressure is indirectly measured (Henik, 1997). Several readings should be taken over several days unless contraindicated by clinical signs of hypertension. With indirect methods, normal blood pressure (mm Hg) in the unsedated cat is 118 (Doppler leg method) to 123/81.2 (mean arterial pressure 96.8) (Henik, 1997) and in dogs is 133/76 (Dinamap on the tail). Antihypertensive therapy is indicated if the indirect systolic pressure or diastolic pressure is greater than 170 or 100 mm Hg, respectively (Henik, 1997).

Returning systolic pressure to normal (i.e., 120 mm Hg) is an unrealistic goal; targeting less than 170 mm Hg in cats is more reasonable (Henik, 1997). Response to therapy should be based on appetite and body weight, ophthalmic examinations, and monitoring of blood pressure. Management of hypertension associated with renal disease should include medical management of that disorder. Additional management includes dietary manipulation (low sodium), diuretics, propranolol, and arterial vasodilators including α-receptor antagonists, CCBs (amlodipine), hydralazine, and ACE inhibitors (Sisson and Thomas, 1995). Dietary changes probably should be withheld until drug therapy is stabilized.

Amlodipine is probably the preferred medication for treatment of systemic feline hypertension, followed by a combination of amlodipine with either an ACE inhibitor or a β-blocker in refractory cases. Hydralazine should be reserved for cases that continue to fail to respond, in part because of the potential for activation of the RAA (Henik, 1997). For cats with severe ocular manifestations or neurologic signs, therapy needs to be more aggressive. Sodium nitroprusside can be given as a constant rate infusion, but the risk of adverse reactions to this arterial and venous dilator requires administration via an infusion pump with constant monitoring. Alternatively, hydralazine coupled with furosemide can be administered, with the addition of a β-blocker (propranolol or atenolol) if response is not sufficient within 12 hours (Henik, 1997). Use of enalapril and amlodipine has been studied in dogs with experimentally induced myocardial infarction. Although both drugs preserved left ventricular volume and function during the healing process, enalapril more effectively limited hypertrophy (Jugdutt, 1997). The role of carvedilol in the management of feline hypertension has not yet been well described.

Long-term management should be based on repetitive monitoring of blood pressure (weekly until the animal is stable at a sufficiently low pressure) and body weight as well as the underlying disease causing hypertension. If renal disease is the underlying cause, monitoring also should include an ocular examination and serum potassium concentrations. Once control is acceptable, monitoring should take place at 3-month intervals. Multiple drug combinations are more likely to be associated with adverse effects (including sleeping, ataxia, and anorexia).

Cardiac Arrhythmias

Supraventricular Arrhythmias

Supraventricular Premature Contractions

Ectopic foci that generate premature contractions in the region of the sinoatrial node, atria, atrioventricular node, or junctional tissue generally are not serious enough to cause clinical signs and, as such, require no medical therapy. If clinical signs are evident, therapy should be directed toward the underlying disease. If therapy is deemed necessary, drugs are selected for their ability to slow atrioventricular nodal conjunction (digitalis glycosides, β-blockers, or CCBs). Drugs associated with negative inotropic effects should be used cautiously if myocardial failure is associated with the supraventricular premature contraction.

Supraventricular Tachycardias

Supraventricular tachycardia includes sinus, atrial, or junctional tachycardia, atrial flutter, and atrial fibrillation. The most likely underlying cause is atrial enlargement due to dilation. Sinus tachycardia is the most common type of supraventricular tachycardia in dogs and is generated by increased sympathetic tone. Treatment includes digitalis glycosides, β-blockers, or CCBs. The most appropriate drug should be based on the underlying cause of the tachycardia. Atrial tachycardia may reflect an autonomic dysfunction (generally not amenable to treatment) or, less commonly, a re-entrant circuit. For re-entrant causes, Class IA antiarrhythmics (especially quinidine), digitalis, or a β-blocker, is indicated. Atrioventricular nodal or junctional tachycardias can be similarly treated.

Atrial fibrillation occurs in the presence of multiple re-entering wavelets; its development is facilitated by a large atrium. The most efficacious antiarrhythmic drugs are those that increase the wavelength (distance traveled by the depolarization impulse during the refractory period). Treatment may be unnecessary if the ventricular rate is less than 150 bpm in asymptomatic dogs with no evidence of cardiac disease. Treatment of atrial fibrillation should focus on slowing the ventricular response such that cardiac filling improves and myocardial oxygen demand decreases. In

jured and ischemic tissues (e.g., due to hypovolemic or cardiogenic shock) also lead to the release of vasoactive and procoagulant mediators. Vascular occlusive diseases such as saddle thrombi and pulmonary thromboembolism (e.g., dirofilariasis) also cause distributive shock (Muir, 1998). With sepsis as an example, initially distributive shock might be "warm" in that blood flow is increased in peripheral tissues. As shock progresses and venous pooling continues, fluid is lost from the vascular space, venous return decreases, cardiac output decreases, and tissues become underperfused or "cool."

Pathophysiology

Ideally, treatment of shock should focus on early reversal based on the underlying cause. As shock progresses, the underlying pathophysiology is the same, and treatment is oriented toward prevention and reversal of inadequate tissue perfusion. Some type of damage is likely to occur in any tissue subjected to a period of hypotension (mean arterial blood pressure <50 mm Hg). These include cell ischemia, inadequate oxygen delivery, and the generation of proinflammatory/procoagulant mediators (Muir, 1998).

Sequelae of Cellular Ischemia

Tissues suffer damage form inadequate tissue oxygenation within 5 to 10 minutes, and the damage is irreversible at 15 to 20 minutes (Muir, 1998). Mitochondrial dysfunction accompanies ATP depletion, leading to anaerobic metabolism and lactic acid accumulation. Cell membrane (ATPase) pumps become disrupted, and intracellular destructive enzymes are released. Accumulation of intracellular calcium leads to the activation of enzymes that disrupt cellular homeostasis. Intracellular sodium and chloride increase, and magnesium and potassium decrease. Adenosine triphosphate breakdown yields hypoxanthine and generation of xanthine oxidase (converted from xanthine dehydrogenase), which produces oxygen free radicals (Muir, 1998). With reperfusion, hyperemia occurs once blood flow is reestablished if the period of impaired oxygenation or poor tissue perfusion is short. The duration of hyperemia is determined by the extent of mediator release (potassium, hydrogen, NO, adenosine, adrenomedullin). On the other hand, if blood flow is less than 20% of normal for longer than 5 minutes, reperfusion after perfusion failure leads to reoxygenation injury. Injury reflects the production of self-destructive enzymes and metabolites and derangements in blood clotting (Muir, 1998). Together, the consequences of reperfusion injury include uneven distribution of blood flow and focal ischemia (perhaps exacerbated by inappropriate thrombosis), swelling of capillary endothelial cells and subsequent plugging by leukocytes migrating to the area, and increased microvascular viscosity and interstitial edema (Muir, 1998).

Oxygen Free Radicals

The generation of oxygen free radicals by mitochondria, macrophages, and neutrophils sets the stage for reperfusion injury should blood flow be re-established following a sufficiently long period of poor perfusion, causing perhaps the most detrimental sequelae of shock (Muir, 1998). Xanthine oxidase metabolizes molecular oxygen into radicals such as superoxide anion, hydrogen peroxide, and the hydroxyl radical (see Chapter 16). Enzymes that normally scavenge oxygen free radicals (superoxide dismutase, catalase, and glutathione) are overwhelmed as tissues reperfuse. Production of oxygen free radicals is exacerbated by mediators released in response to oxygen free radicals, including cytokines (including tumor necrosis factor), interleukins (which also induce procoagulant activity), and prostaglandins (Muir, 1998).

Role of Nitric Oxide

Nitric oxide can be either protective or detrimental in the patient with sepsis and endotoxemia. Under basal physiologic conditions, it serves as a free oxygen radical scavenger, limiting toxicity associated with superoxide and other radicals. Inhibition of platelet aggregation and leukocyte adhesion limits ischemia-reperfusion injuries (Parratt, 1998). During shock, large amounts of iNOS are formed; as such, NO becomes a major contributor to the pathophysiology of shock (Parratt, 1998; Muir, 1998). Peroxynitrous acid, generated from the reaction of NO with oxygen free radicals, destroys cellular macromolecules, causing mitochondrial and cell membrane dysfunction, production of prostaglandins, and programmed cell death (apoptosis). The coagulation cascade is activated, ultimately leading to disseminated intravascular coagulation. Arteriovenous shunting (possibly caused by iNOS) contributes to maldistribution of blood flow, particularly in endotoxic and other septic shock and may be the cause of irreversibility (Muir, 1998).

Thus, although the initial responses of the body to iNOS might lead to important compensatory responses, ultimately the responses may prove to be detrimental. Yet, inhibition of NOS is undesirable because systemic vascular resistance is improved only at the cost of loss of blood flow to vital organs. Platelet aggregation increases, along with the risk of thrombus formation and disseminated intravascular coagulation (Muir, 1998). Analogues of L-arginine, such as L-NAME (*N*-nitro-L-arginine methyl ester) competitively inhibit NO production by either cNOS or iNOS from L-arginine. Treatment of human patients in septic shock with L-NAME, however, led to pulmonary hypertension and reduced cardiac output (Avontuur et al., 1998). Drugs that selectively inhibit iNOS but not cNOS may be a more appropriate focus of investigation.

Gastrointestinal Barrier

The sequelae of ischemia and hypoxia in the gut have profound clinical implications for the patient undergoing shock. Potent vasoconstrictors (endothelins), cytokines, and other mediators act in concert with leukocyte migration and epithelial necrosis to increase capillary permeability, transcapillary fluid filtration, and interstitial edema. Diarrhea is a common clinical complication of resuscitation from shock and may indicate the loss of the protective mucosal barrier in the gastrointestinal tract. Bacterial translocation and endotoxin absorption result in release of mas-

function. It is beyond the scope of this chapter to discuss the causes of and recognition of the need for CPCR. Obviously, prevention is the key to success, and treatment of underlying diseases likely to cause cardiopulmonary arrest should be reviewed. The focus of this discussion is on drugs used in CPCR. Which drugs are proper and when their use is indicated in the patient are controversial. Cardiac rather than respiratory arrest is discussed. The pharmacologic effects, side effects, and other pertinent clinical pharmacologic data for each of the drugs has been discussed elsewhere; discussion here is limited to the use of the drugs during or immediately after CPCR.

"Crash Cart" Drugs

Drugs that should be carried in a "crash cart" include epinephrine, atropine, magnesium chloride, naloxone, lidocaine, sodium bicarbonate, and bretylium tosylate (Wingfield, 1996).

Epinephrine remains the mainstay of acute cardiac life support. It is intended to promote systemic vasoconstriction such that blood flow is diverted to the coronary and cerebral circulation. It is indicated for pulseless ventricular tachycardia, ventricular fibrillation, electromechanical dissociation (pulseless electrical activity), and ventricular asystole. The standard dose is 10 to 20 μg/kg (1 mg in humans) or 10 mL of a 1:10,000 solution repeated every 3 to 5 minutes. The optimal dose may be very high, ranging from 0.45 to 2 mg/kg. For humans, the American Heart Association has recommended a fivefold increase in the dose to 5 mg if there is no response to the initial 1 mg dose (Marini and Wheeler, 1997).

Atropine has little indication in CPCR with the exception of bradycardia, pulseless electrical activity, and ventricular asystole. The dose for electromechanical dissociation and asystole is 1 mg IV, repeated every 3 to 5 minutes. In people, complete vagal blockade occurs at 0.04 mg/kg (3 mg); this dose should be avoided. Likewise, a total dose less than 0.5 mg can cause parasympathomimetic effects and also should be avoided (Marini and Wheeler, 1997).

Isoproterenol is a pure, nonselective β-agonist drug. As such, it is a positive inotrope but can also cause peripheral vasodilation. It will increase myocardial oxygen demand. Currently, its use is limited to bradyarrhythmias that do not respond to atropine (Wingfield, 1996).

Bicarbonate provides little benefit and may in fact harm patients in metabolic acidosis. Acidosis associated with cardiac arrest is best treated with ventilatory and circulatory support. Potentially harmful effects of bicarbonate include arrhythmogenic alkalemia, increased generation of CO_2, hyperosmolarity, hypokalemia, paradoxical CNS and myocardial intracellular acidosis, and a leftward shift in the oxyhemoglobin dissociation curve, limiting delivery of O_2 to tissues (Marini and Wheeler, 1997). When used, bicarbonate therapy ideally should be guided by blood gas analysis ($pH < 7.15$ to 7.2) (Marini and Wheeler, 1997). Indications or situations in which bicarbonate may prove beneficial for humans requiring CPCR include hyperkalemia, tricyclic antidepressant overdose, prolonged cardiac arrest (protracted hypoperfusion-induced acidosis), and postresuscitation, bicarbonate responsive, and anaerobic lactic acidoses (Marini and Wheeler, 1997). Sodium bicarbonate (1 mEq/kg IV) may be used after epinephrine in patients suffering from a prolonged cardiac arrest who have shown improvement in cardiovascular or cerebral recovery. It should be followed by correction of the any deficit (monitored) which is greater than 5 mEq/kg. The bicarbonate-induced hypercarbia tends to be transient and generally harmless to the heart if used in conjunction with epinephrine (Wingfield, 1996).

Calcium administration does not appear to enhance cardiac performance during CPCR. Ischemia associated with cardiac arrest causes intracellular accumulation of calcium, which can disrupt membranes and uncouple oxidative phosphorylation. Calcium can cause coronary vasospasm and will exacerbate the arrhythmic tendency of the unstable myocardium and impair relaxation (Marini and Wheeler, 1997; Wingfield, 1996). It will also exacerbate digoxin toxicity. Calcium causes precipitation when combined with sodium bicarbonate. Calcium should be avoided except in cases of prolonged cardiac arrest or absent or ineffective pump activity. Calcium chloride (10% solution contains 100 mg/mL) is associated with the longest and most predictable increase in plasma ionized calcium (Wingfield, 1996). In human patients, 1 g of calcium chloride (approximately 15 mg/kg) is generally sufficient, although toxicity may occur at this dose. Other indications for calcium include hyperkalemia, ionized hypocalcemia, and CCB overdose (Marini and Wheeler, 1997).

Crystalloids (including hypertonic resuscitation and balanced electrolyte solutions) are indicated if the cause of cardiac arrest is hypovolemia. Inappropriate fluid load can, however, contribute to decreased cerebral blood flow and decreased coronary blood flow (Wingfield, 1996). The production of lactic acid will be enhanced in critically ill hyperglycemic patients, which can lead to or contribute to cell injury. Dextrose infusions are considered by the American Heart Association to be harmful to humans (Marini and Wheeler, 1997). As such, dextrose-containing fluids should be avoided. Isotonic saline or Ringer's lactate is preferred as the resuscitation fluid.

Several routes of drug administration can be used to support resuscitation. Central venous catheter placement is ideal for immediate drug delivery to the heart. A sufficient bolus of a compatible isotonic fluid should follow any drug administered through peripheral tubing. Intracardiac injections probably offer no increased benefit compared with central IV administration. Potential complications include cardiac tamponade, coronary vessel laceration, and pneumothorax. Intracardiac bolus may destabilize the electrical properties of the heart.

Intratracheal (IT; endotracheal) administration is an effective alternative route to central IV administration for selected drugs during CPCR (Wingfield, 1996). Drugs are, however, administered (to humans) in 10 to 20 mL of liquid in order for the drug to reach the alveoli, where they will be subsequently absorbed. Doses of all drugs administered IT should be increased by 2- to 2.5-fold. The duration of action of the drugs may be longer after IT than IV administration. Drugs shown to be effective after IT administration include epinephrine, lidocaine, atropine, and naloxone. There are several drugs that should not be given after IT administration due to the risk of tissue damage. Examples include sodium bicarbonate (depletes surfactant),

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31 Drugs Affecting the Respiratory System

Dawn Merton Boothe

- NORMAL RESPIRATORY PHYSIOLOGY
  - Airway Caliber Changes
  - Respiratory Defense Mechanisms
- PATHOGENESIS OF INFLAMMATORY RESPIRATORY DISEASES
- INFLAMMATORY MEDIATORS IN THE RESPIRATORY TRACT
  - Histamine
  - Serotonin
  - Prostaglandins and Leukotrienes
  - Platelet-Activating Factor
- DRUGS USED TO MODULATE THE RESPIRATORY TRACT
  - Bronchodilators and Anti-inflammatory Drugs
    - β-Receptor Agonists
    - Methylxanthine Derivatives
    - Anticholinergic Drugs
  - Mast Cell Stabilizers
    - Cromolyn
    - Calcium antagonists
  - Drugs that Target Inflammatory Mediators
    - Drugs that Target Leukotrienes
    - Nonsteroidal Anti-inflammatory Drugs
    - Antihistamines
- ANTITUSSIVES
  - Narcotic Antitussives
    - Codeine
    - Hydrocodone
  - Non-narcotic Antitussives
    - Butorphanol
    - Dextromethorphan
    - Noscapine
    - Peripheral Bronchodilators
- MUCOKINETICS
  - Pharmacologic Effects
  - Disposition of *N*-Acetyl-L-Cysteine
  - Adverse Effects
- EXPECTORANTS
  - Iodide Preparations
  - Stimulant Expectorants
- DECONGESTANTS
- AEROSOLIZATION AS A ROUTE OF DRUG ADMINISTRATION
- DRUG THERAPY OF SPECIFIC DISEASES OF THE RESPIRATORY TRACT
  - Therapy of Fungal Infections of the Nose
  - Therapy of Disorders of the Trachea
    - Tracheitis
    - Structural Disorders of the Trachea
  - Bronchial Diseases
    - Canine Infectious Tracheobronchitis
    - Feline bronchial Diseases
    - Canine Bronchitis
  - Pulmonary Diseases
    - Bacterial Pneumonia
    - Mycotic Pneumonia
    - Parasitic Disease
    - Immune-Mediated Diseases
    - Vascular Diseases
    - Miscellaneous
  - Diseases of the Pleura
  - Empyema

NORMAL RESPIRATORY PHYSIOLOGY

Airway Caliber Changes

Nervous innervation to the smooth muscle of the respiratory tract is complex. The parasympathetic system provides the primary efferent innervation, with acetylcholine as the primary neurotransmitter (Moses and Spaulding, 1985; Slonim and Hamilton, 1987). These fibers are responsible for the baseline tone of mild bronchoconstriction that characterizes the normal respiratory tract. The sympathetic system, which balances these effects by stimulating bronchodilation through β_2-receptors (Scott et al., 1991; Gustin et al., 1989; Chand and Deroth, 1979). In contrast, α-adrenergic stimulation can contribute to bronchoconstriction (Moise and Spaulding, 1981; Slonim and Hamilton, 1987; Gustin et al., 1989) A third, largely understood nervous system, referred to as the nonadrenergic, noncholinergic system, or purinergic system, also innervates bronchial smooth muscle (Inque et al., 1989; Moses and Spaulding, 1985). This system mediates bronchodilation via vagal stimulation. The afferent fibers of this system are probably irritant receptors, and, although the neurotransmitter has not yet been conclusively identified, vasoactive intestinal peptide has been implicated in the cat (Altiere and Diamond, 1984; Altiere et al., 1984). Malfunction of this system has been associated with bronchial hyperreactivity, which often characterizes asthma (Inque et al., 1989).

The intracellular mechanisms that transmit signals from the nervous system to smooth muscle depend, in part on changes in the intracellular concentration of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) (Fig. 31–1). The effects of these two secondary messengers are reciprocal such that the increased intracellular concentration of one is associated with a decreased concentration of the other. Cyclic AMP-induced bronchodilation is decreased by α-adrenergic stimulation and increased by β_2-receptor stimulation (Scott et al. 1991). In contrast, cGMP-induced bronchoconstriction is increased by stimulation of muscarinic (cholinergic) and, indirectly, histaminergic receptors (see Fig. 31–1). The relative sensitivity of bronchial smooth muscle to histamine-induced and acetylcholine-induced bronchoconstriction varies with the location and species (Chand and Deroth, 1979; Derksen et al., 1985; Downes et al., 1986). Peripheral airways in dogs are more susceptible than in cats to acetylcholine; cat airways, in general, are more sensitive to acetylcholine than histamine (Colebatch et al., 1966). Smooth muscle receptors are also susceptible to stimulation by a variety of chemical mediators (see Fig. 31–1), which may also modulate cAMP and cGMP (Townley et al., 1989; Soler et al., 1990; Gray et al., 1989).

Control of bronchial smooth muscle tone is very complex and depends on input from sensory receptors. At least five types of sensory receptors have been identified in cat lungs, all of which can be classified as irritant (or mechanoreceptor), stretch, or J-receptors (Inque et al., 1989). All appear to be innervated by the parasympathetic

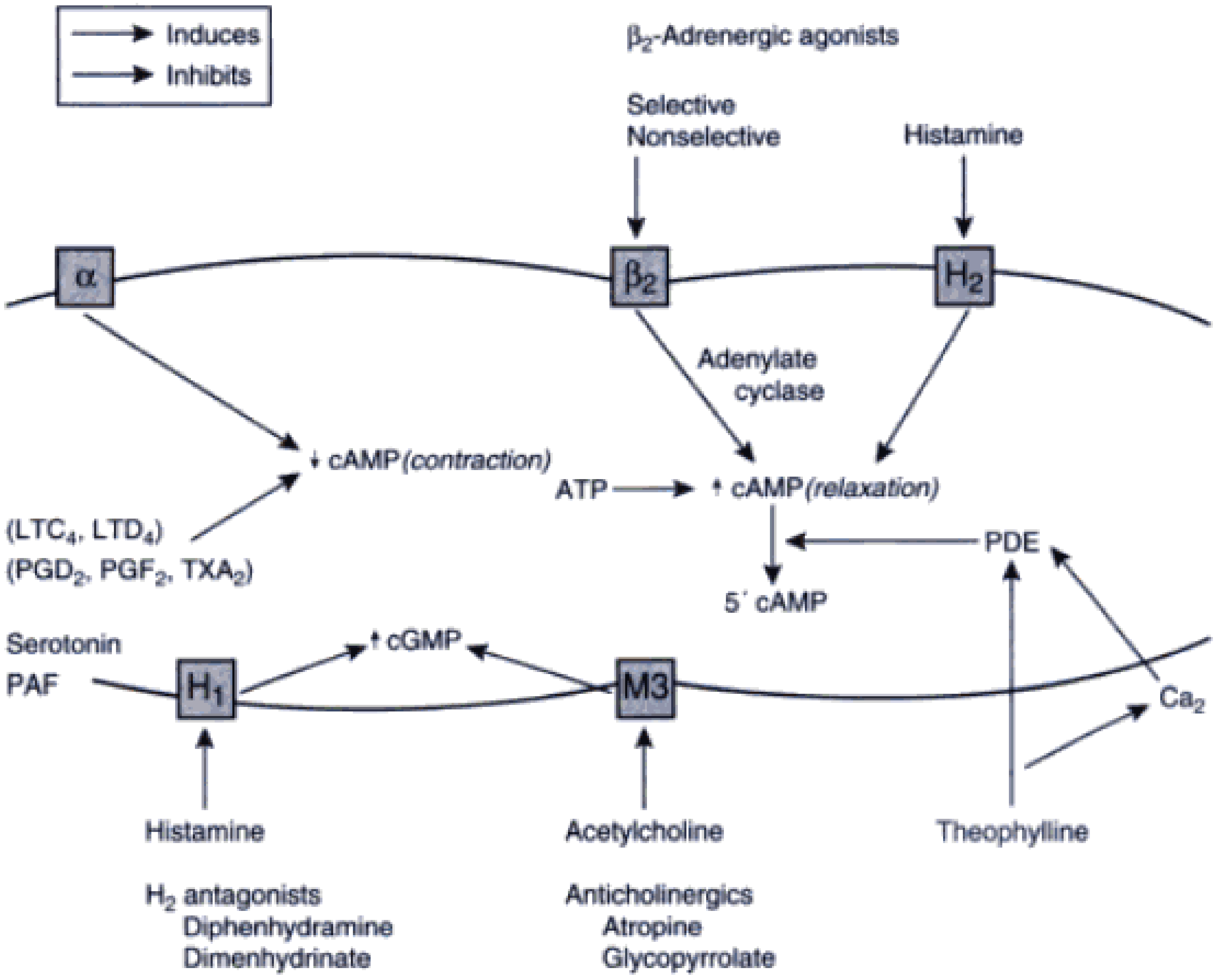

Figure 31–1. Factors determining bronchial smooth muscle tone. Reciprocal changes in cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) determine muscle tone. Contraction occurs when cAMP levels are decreased by events such as α-adrenergic stimulation or when cGMP levels increase in response to muscarinic receptor (M3) stimulation by acetylcholine or H_1-receptor stimulation by histamine. Calcium (Ca^{2+}) and several mediators can also induce bronchoconstriction. Increased cAMP levels induced by β_2-adrenergic or histamine (H_2) receptor stimulation counteract muscle contraction. Inhibition of phosphodiesterase (PDE) also causes increase cAMP. Although the effects of most inflammatory mediators are best counteracted by preventing their release (see Fig. 31–3), several drugs may be used to antagonize smooth muscle contraction regardless of the etiology. LTC, LTD = leukotrienes C and D; PAF = platelet-activating factor; PGD_2, PGF_2 = prostaglandins D_2 and F_2; TXA_2 = thromboxane.

system. Irritant receptors, located beneath the respiratory epithelium, occur in the upper airways (Slonim and Hamilton, 1987) and, in cats, as far peripherally as the alveoli (Moses and Spaulding, 1985). Physical, mechanical, or chemical stimulation of these receptors results in tachypnea, bronchoconstriction, and cough. Airflow velocity appears to be the most critical factor determining stimulation of irritant receptors in the upper airways (Moses and Spaulding, 1985). Airway constriction sufficient to cause airflow velocity to exceed a specific threshold results in a vagally mediated cough reflex and bronchoconstriction. Airways can also be occluded by mucus and edema or by chemical mediators released during upper airway infections (Inque et al. 1989).

Respiratory Defense Mechanisms

In addition to the cough and sneeze reflexes, two other systems provide the major defense of the respiratory tract against invading organisms or foreign materials: the mucociliary apparatus and the respiratory mononuclear phagocyte system (Slonim and Hamilton, 1987). The mucociliary apparatus (Fig. 31–2) is the first major defense and consists of the ciliary lining of the tracheobronchial tree and the fluid blanket surrounding the cilia. Nervous innervation to the cilia has not yet been identified. Although ciliary activity increases with β-adrenergic stimulation, this may simply reflect the sequelae of β-adrenergic stimulation on respiratory secretions (Blair and Woods, 1969). Two types of secretions form the fluid blanket of the respiratory tract. The cilia must be surrounded by a low-viscosity, watery medium to maintain their rhythmic beat. A more mucoid layer lies on top of the cilia and serves to trap foreign materials inspired with air. The synchronous motion of the cilia causes the cephalad movement of the mucous layer and any trapped materials.

Changes in the viscoelastic properties of mucus such

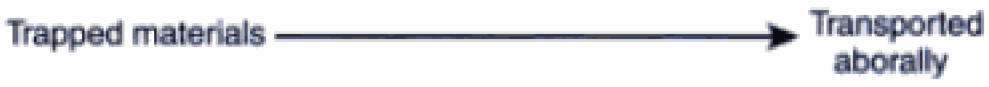

Figure 31–2. The mucociliary apparatus represents the first line of defense for pathogens entering the respiratory tract. Cilia are bathed in a water or sol layer. When the cilia beat in synchrony, the movements send forward (orally) the mucoid or gel layer that lies on top of the cilia. Materials trapped in this layer also move forward to be either swallowed or expectorated.

mediated by H_2 receptors and would be inhibited by H_2-receptor antagonists (Chand, 1981).

Serotonin

Serotonin (5-hydroxytryptamine [5-HT]) is released during mast cell degranulation (Barnes et al., 1988). Although serotonin does not appear to be an important mediator of human or canine bronchial asthma, both the central and peripheral airways in cats are very sensitive to its bronchoconstrictive effects after aerosolization or intravenous administration (Colebatch et al., 1966). Constriction may reflect interaction with serotonin receptors or enhanced release of acetylcholine. Serotonin may also cause profound vasoconstriction of the pulmonary vasculature and microvascular leakage (Barnes et al., 1988).

Prostaglandins and Leukotriens

Prostaglandins (PGs) and leukotrienes (LTs) are eicosanoids that are formed when phospholipase A_2 is activated in the cell membrane in response to a variety of stimuli (see Fig. 31–3). Arachidonic acid (AA) is subsequently released from phospholipids and enters the cell. In the cell it is converted by cyclooxygenases to inflammatory, but unstable cyclic endoperoxides. The actions of various synthetases and isomerases on the endoperoxides result in the final PG products, including PGE_2, $PGF_{2\alpha}$, PGD_2, prostacyclin or (PGI_2), and thromboxane (TXA_2). The amount of each PG produced in the lung varies with the cell type and species. The effects of the various PGs tend to balance one another. PGD_2, $PGF_{2\alpha}$, and TXA_2 cause bronchoconstriction, whereas PGE_1 and to a lesser extent PGI_1 cause bronchodilation (Barnes et al., 1988; Moses and Spaulding, 1985). Bronchoconstriction induced by PGD_2 is about 30 times as potent as that induced by histamine.

Imbalances between PGs may be important in the pathogenesis of bronchial disease. Both PGD_2 and TXA_2 have been implicated in immediate bronchial airway hyperreactivity (Barnes et al., 1988). Thromboxane A_2 appears to be the predominant AA metabolite produced by cat lungs (McNamara et al., 1989), although other PG mediators are also important (McNamara et al., 1989).

Lipoxygenases in the lung catalyze the conversion of AA to hydroperoxyeicosatetraenoic acid (HPETEs), which are further metabolized to several hydroxy acids (HETEs) and LTs (see Fig. 31–3). All of these products are biologically active in the respiratory tract (see Table 31–1) (Barnes et al., 1988), and some are the most potent inflammagens known. Antigenic challenge results in the selective activation of 5-lipoxygenase, the enzyme that ultimately results in the formation of LTC_4 and LTD. These LTs are the components of slow reactive substance, an important mediator released in the lungs during anaphylaxis (Barnes et al., 1988). Eosinophils also preferentially activate 5-lipoxygenase (Barnes et al., 1988). Bronchial smooth muscle contraction and microvascular permeability mediated by LTC_4 and LTD_4 is 100- to 1000-fold more potent than that induced by histamine. Both LTs are potent stimulators of mucous release in the dog but appear to be less potent in the cat (Barnes et al., 1988). Leukotriene B_4, produced by macrophages, is the most potent chemotactant of the LTs.

Platelet-Activating Factor

Platelet-activating factor (PAF) is also formed after activation of phospholipase A_2 in all membranes. It is potent, dose-independent constrictor of human airways, and it is the most potent agent thus far discovered in causing airway microvascular leakage (Barnes, 1988, 1989). PAF is also a potent chemotactant for platelets and eosinophils, both of which are a rich source of PAF. The effects of PAF may be mediated through LTs. PAF has been implicated as the cause of the sustained bronchial hyperresponsiveness that characterizes asthmatics (Barnes, 1989). The role of PAF in feline and canine respiratory diseases has not been addressed. Eosinophils are, however, a major cell type associated with feline bronchial disease and some canine diseases (Moise et al., 1989), and it is likely that PAF is an important inflammatory mediator.

DRUGS USED TO MODULATE THE RESPIRATORY TRACT

The syndrome of chronic bronchial disease is best treated by breaking the inflammatory cycle while immediately relieving bronchoconstriction. Thus, anti-inflammatory drugs and bronchodilators represent the cornerstone of therapy for many bronchial diseases. Other categories of drugs that are effective for the management of respiratory diseases, particularly in small animals, include antitussives, respiratory stimulants, and decongestants.

Bronchodilators and Anti-inflammatory Drugs

Because of a shared mechanism of action, most drugs that induce bronchodilation also reduce inflammation. Bronchodilators reverse airway smooth muscle contraction by increasing cAMP, decreasing cGMP, or decreasing calcium ion concentration (see Fig. 31–1). In addition, these drugs also decrease mucosal edema and are anti-inflammatory because they tend to prevent mediator release from inflammatory cells (see Fig. 31–3). Rapidly acting bronchodilators include β-receptor agonists, methylxanthines, and cholinergic antagonists.

β-Receptor Agonists

β-Receptor agonists are the most effective bronchodilators because they act as functional antagonists of airway constriction, regardless of the stimulus (Barnes, 1988; Daemen et al., 1988; Papich, 1986a; Reed and Kelly, 1990). Large numbers of β_2-receptors are located on several cell types in the lung, including smooth muscle and inflammatory cells (Scott et al, 1991). The interaction between a β-agonist and receptor causes a conformational change in the receptor and subsequent activation of adenyl cyclase on

to increase hepatic enzymes (and thus is safer) among different species and can be administered less frequently (every 8 to 12 hours compared with every 6 to 8 hours for zileuton). Although anecdotal reports of efficacy and safety exist for dogs and cats, no written report appears available. The role of LTs in feline asthma is now being elucidated; the drugs appear to be effective for dogs. Zafirlukast may inhibit some hepatic drug metabolizing enzymes.

Nonsteroidal Anti-inflammatory Drugs

The role of nonsteroidal anti-inflammatory drugs (NSAIDs) in the treatment of respiratory inflammatory diseases needs to be defined (Parratt and Sturgess, 1974; Wasserman, 1988). Both LTs and PGs are important in the pathophysiology of inflammatory diseases. Although NSAIDs effectively block PGs through inhibition of cyclooxygenase, they do not appear to have any effect on lipoxygenase and therefore production of LTs. They have no effect on other chemical mediators of inflammation. Additionally, NSAIDs nonselectively block all PGs, including those that provide some protection during periods of bronchoconstriction (Walker et al., 1982). Some studies have shown that LT production increases in response to NSAID therapy, perhaps by providing more AA for lipoxygenase metabolism.

Currently, the use of NSAIDs for the treatment of respiratory diseases in small animals is limited to aspirin therapy as treatment for thromboembolism associated with heartworm disease (Keith, 1983; Rawlings et al., 1983). Aspirin is the preferred NSAID because at low doses it irreversibly inhibits TXA_2, an important contributor to pulmonary arterial vasoconstriction that accompanies thromboembolism. Current efforts in NSAID research are oriented toward identifying drugs that successfully inhibit both arms of the AA metabolic cascade or specific PG or LT inhibitors. The use of selective TXA_2 inhibitors for selected feline respiratory diseases is an example (McNamara et al., 1989).

Antihistamines

Antihistaminergic drugs have not proved clinically useful in the control of small animal or human respiratory diseases (Eiser et al., 1981; Moise and Spaulding, 1981; Zenoble, 1980). Several observations support their lack of efficacy. Although not proven, the number of histamine receptors located in the airways and the proportion of H_1 to H_2 receptors may not be sufficient to induce a response similar to that in disease. Antihistaminergic drugs act to block target receptors from responding to histamine; however, the drugs do nothing to prevent release of histamine or other mediators from any inflammatory cell. The newer antihistamines (H_1), loratadine and cetirizine, are exceptions, drugs that also decrease histamine release from basophils (Chyrek-Borowska et al., 1995). Although well tolerated, these drugs apparently have not been studied for efficacy or safety in animals. This may in fact be the major reason for lack of clinical efficacy of antihistaminergic drugs; mediators other than histamine released during mast cell degranulation and by other inflammatory cells are often much more potent than histamine (Krauer and Krauer, 1977). Finally, blockade of histamine receptors is competitive and can be overwhelmed by high concentrations of histamine. The use of H_1 blockers may be detrimental in animals with chronic disease because of their effects on airway secretions (Barnes et al., 1988). The role of H_2 receptors in bronchodilation, mucous secretion, and inflammation suggests that H_2-receptor blockers should also be used with caution (Barnes et al., 1988; Chand, 1981). An exception to antihistamine use for treatment of respiratory infalmmatory disease might be made for the use of cyproheptidine, an antiserotinergic, antihistaminergic drug. Because feline airways are exquisitely sensitive to the constrictor effects of serotonin, this drug may prove particularly useful in cats either alone or as an adjunct to bronchodilators or glucocorticoids (Padrid et al., 1995).

ANTITUSSIVES

The goal of antitussive therapy is to decrease the frequency and severity of cough without impairing mucociliary defenses. Whenever possible, the underlying cause should be identified and treated. Cough suppressants should be used cautiously and are contraindicated if the cough is productive (Slonim and Hamilton, 1987). Irritant, and perhaps chemoreceptors and stretch receptors, initiate the cough reflex (McKiernan, 1983; Slonim and Hamilton, 1987). Bronchoconstriction is probably the most frequent and important cough stimulus. The cough reflex can be blocked peripherally, either by facilitating removal of the irritant with mycolytics or expectorants or by blocking peripheral receptors to induce bronchodilation, or it can be blocked centrally at the cough center in the medulla (Fig. 31–4) (Roudebush, 1982; Slonim and Hamilton, 1987).

Centrally active antitussives are classified as narcotic and non-narcotic drugs (Roudebush, 1982; Irwin et al., 1993).

Narcotic Antitussives

Narcotic antitussives depress the cough center sensitivity to afferent stimuli. They can, however, be associated with strong sedative properties, as well as constipation when administered chronically. Morphine, codeine, and hydrocodone are the narcotics most commonly used to control coughing. As Class II drugs, each is subject to the Controlled Substances Act of 1970 and can be used for cough suppression in both dogs and cats.

Codeine

Codeine is the prototype narcotic antitussive and is one of the most effective drugs available to suppress the cough reflex. Codeine phosphate and codeine sulfate can be used either alone or in combination with either peripheral cough suppressants or decongestants. Over-the-counter preparations are available for human use. Compared with morphine, codeine is equally effective as a cough suppressant but is less suppressing to other central centers and causes less constipation. Side effects of codeine include nausea and constipation. Codeine is also addressed in Chapter 22.

Hydrocodone

Hydrocodone is a more potent antitussive than codeine but causes less respiratory depression. It is probably the most

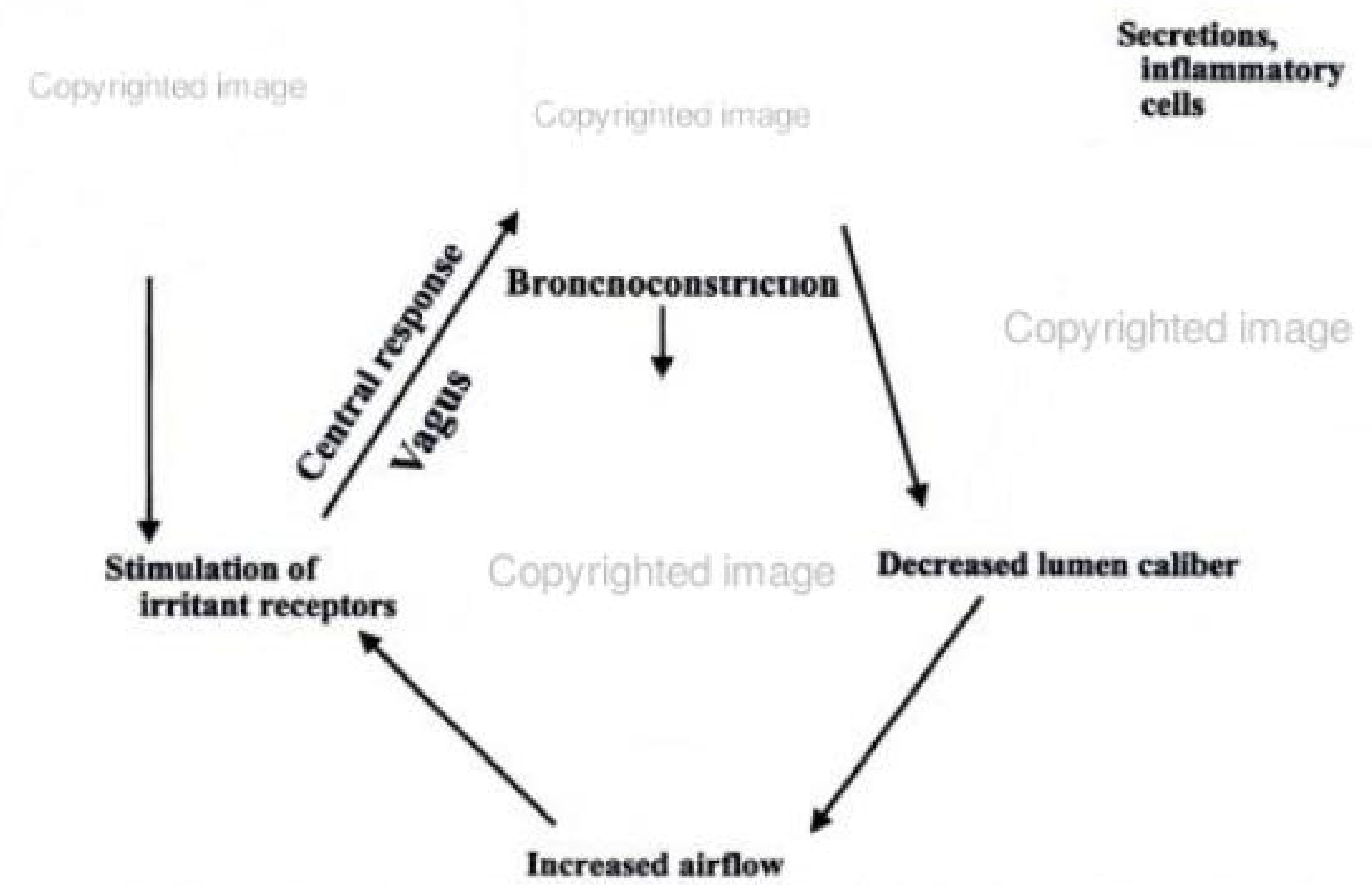

Figure 31–4. The most potent stimulus for the cough reflex is decreased airway caliber size. The subsequent increase in airflow velocity irritates stretch receptors. The vagus nerve serves as the afferent and efferent limbs of the cough reflex, which is mediated centrally by the respiratory center in the medulla. Accumulation of debris and inflammatory mediators can either irritate receptors or decrease airway luminal caliber. Cough is accompanied by bronchoconstriction, which can further exacerbate coughing.

commonly used antitussive for dogs. Hydrocodone bitartrate is a hydrolysis product of dihydrothebaine.

Butorphanol

Butorphanol tartrate is probably more commonly used as an analgesic. Reclassified as a Schedule IV drug, it is now subject to the narcotics act. It is approved for use as an antitussive for dogs. As an antitussive, it is 100 times more potent than codeine and 4 times more potent than morphine (Gingerich et al., 1983). In dogs, after subcutaneous administration, butorphanol concentrations peak at 1 hour. Mean half-life is 1.7 hours, with a duration of activity of 4 hours or more. Butorphanol is characterized by a wide safety margin. The LD_{50} in dogs after intramuscular administration is 20 mg/kg (Christie et al., 1980). Therapeutic concentrations cause minimal cardiac or respiratory depression. Side effects include sedation, which can be significant and desirable, nausea, some diarrhea, and appetite suppression. The narcotic agonist/antagonist butorphanol tartrate is a potent antitussive when given orally or parenterally in dogs and cats (Hosgood, 1990).

Non-narcotic Antitussives

Non-narcotic antitussives commonly used in veterinary include the narcotic agonist/antagonist butorphanol and dextromethorphan.

Dextromethorphan

Dextromethorphan hydrobromide is a semisynthetic derivative of opium that lacks its narcotic properties. Sedation is unusual after its use. Only the L-isomer has antitussive activity, which is similar to codeine in potency. Its onset of action is rapid, being fully effective within 30 minutes after oral administration. Dextromethorphan is a non-narcotic opiod commonly found in over-the-counter cough preparations. It is used for small animals with minimal sedation, and its antitussive efficacy is equal to that of codeine. It can be used safely in cats. Studies in humans have shown that the combination of dextromethorphan with a bronchodilator is superior to dextromethorphan alone (Tukianinen et al., 1986).

Noscapine

Noscapine is a nonaddictive opium alkaloid (benzylisoquinolone) that has antitussive effects similar to codeine (Brain, 1983). It use for small animals appears to be limited.

Peripheral Bronchodilators

Bronchodilators (previously discussed) are powerful peripheral antitussives because they relieve irritant receptor stimulation induced by mechanical deformation of the bronchial wall during bronchoconstriction. Ephedrine peripherally induces bronchodilation and as both a bronchodilator and decongestant is a common constituent of over-the-counter cough preparations. Theophylline and isoproterenol are also common ingredients found in some preparations. Other peripheral antitussives include mucokinetic agents and hydrating agents (Roudebush, 1982).

MUCOKINETICS

Mucokinetic drugs facilitate the removal of secretions from the respiratory tree. They are indicated for conditions associated with viscous to inspissated pulmonary secretions such as are commonly associated with chronic bronchial diseases. Mucokinesis can be induced by drugs that improve ciliary activity (e.g., β-receptor agonists and methylxanthines) or by drugs that improve the mobility of bronchial secretions by changing viscosity. Viscosity of bronchial secretions can be decreased by hydration (e.g., sterile or bacteriostatic water or saline), increasing pH (e.g., sodium bicarbonate), increasing ionic strength (sodium bicarbonate and saline), or by rupture of sulfur (S–S) linkages in the mucus (e.g., acetylcysteine or iodine). Hydrating agents can be administered parenterally (i.e., isotonic crystalloids) or by aerosolization. Home aerosolization can be easily achieved with a humidifier or steamed bathroom or with a commercially available aerosolizer. The efficacy of aerosolization in liquefying airway secretions is controversial (Wanner and Rao, 1980), with the greatest benefit occurring in the upper airways. Bland aerosols such as water and saline can actually be detrimental to mucociliary function (Wanner and Rao, 1980). The efficacy of ionic solutions or alkaline solutions compared with water on enhanced mucous mobility is controversial (Wanner and Rao, 1980).

Pharmacologic Effects

Acetylcysteine (*N*-acetyl-L-cystein) is the mucolytic drug most widely used by humans (Wanner and Rao, 1980; Ziment, 1988). Although it appears to be efficacious after aerosolization, oral administration has become the preferred route (Ziment, 1988). In Europe, the drug is available in solid and powder dosing forms. Unfortunately, only the solution, which is unpalatable and malodorous, is approved for use in the United States. The powder is available as a chemical reagent from several chemical companies and purchase with application to food or as a capsule might be considered.

Regardless of the route of administration, the mechanism of acetylcysteine reflects destruction of mucoprotein of the disulfide bonds by a free sulfhydryl group. Smaller molecules are less viscid and not able to efficiently bind to inflammatory debris. In addition, *N*-acetylcysteine serves as a precursor to glutathione, a major scavenger of free oxygen radicals associated with inflammation. The drug also appears to induce respiratory tract secretions, probably via a gastropulmonary reflex. At higher oral doses, acetylcysteine will also induce vomiting (Ziment, 1986). Acetylcysteine is often used in combination with aerosolized antimicrobials because it may improve antibacterial penetration of infected mucus (Ziment, 1988). Acetylcysteine improved gas exchange in a study of dogs with experimentally induced methacholine bronchoconstriction (Ueno et al., 1989).

Disposition of N-Acetyl-L-Cysteine

In humans, acetylcysteine is rapidly absorbed from the gastrointestinal tract and extensively distributed to the liver, kidneys, and lungs, where it may accumulate. It is rapidly metabolized by the liver to the natural amino acids cysteine and cystine (Ziment, 1986, 1988). The indications for oral acetylcysteine therapy for people include toxic inhalants (including tobacco smoke), bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, tuberculosis, pneumonia and emphysema, and the adult respiratory distress syndrome. Installation of a 10% to 20% solution has also been used to clean and treat chronic sinusitis (Ziment, 1988). Similar uses are indicated in veterinary patients. Physiotherapy will enhance the efficacy of acetylcysteine. The drug is usually dosed at 125 to 500 mg (about 5 to 10 mg/kg) in human patients. I have used this dose successfully, but have used higher doses (144 mg/kg IV followed by 70 mg/kg 12 hours later) in life-threatening conditions. A twice to three times daily frequency is recommended. I have used the drug to treat pneumonia, chronic bronchial diseases, chronic sinusitis, electrical cord bites, and other respiratory syndromes associated with inflammation.

Adverse Effects

Acetylcysteine therapy is associated with few adverse affects. In humans, doses as high as 500 mg/kg are well tolerated (Ziment, 1986), although vomiting and anorexia can occur. The median LD_{50} in dogs after oral use is 1 g/kg and parenterally, 700 mg/kg. Because it is metabolized to sulfur-containing products, it should be used cautiously for animals suffering from liver disease characterized by hepatic encephalopathy. Aerosolization of *N*-acetylcysteine can cause reflex bronchoconstriction due to irritant receptor stimulation and should be preceded with bronchodilators.

EXPECTORANTS

Expectorants such as potassium iodide are common ingredients in over-the-counter cough preparations. Expectorants increase the fluidity of respiratory secretions through several mechanisms and are often used as adjuvants for the management of cough by facilitating removal of the inciting cause. Bronchial secretions are increased by vagal reflex after gastric mucosa irritation (iodide salts) and directly through sympathetic stimulation or by volatile oils that are partially eliminated via the respiratory tract. Although the combination of expectorants with antitussives in over-the-counter cough preparations may seem irrational, the antitussive drugs in these combination products do not appear to prevent stimulation of the cough reflex induced by liquified secretions commonly included in over-the-counter cough preparations. Their mechanism of action is unknown, although they may be ineffective at the doses used in cough preparations (Papich, 1986b).

Iodide Preparations

Potassium iodide is a saline expectorant capable of increasing secretions by 150%. Ethylenediamine dihydroiodide, used as a nutritional source of iodine in cattle, may be useful for the treatment of mild respiratory diseases. Iodide preparations should not be used in pregnant or hyperthyroid animals or in milk-producing animals. Demulcent expectorants such as syrup are often used as the vehicle for cough medicaments but has no apparent expectorant value. They may, however, be useful for treatment of cough caused by pharyngeal irritation.

Stimulant Expectorants

Stimulant expectorants are used more commonly for coughing associated with chronic bronchial diseases. Guaiacol and its glyceryl ether guaifenesin (glyceryl guaiacolate) are wood tar derivatives. Neither the volume of viscosity nor respiratory secretions appear to change after treatment with guaifenesin, although airway particle clearance increases in bronchitic human patients.

DECONGESTANTS

The indications for decongestants include sinusitis of allergic or viral etiologies and reverse sneezing or other complications of postnasal drip. Information regarding the use of decongestants in animals is largely based on extrapolation from human patients for which allergic rhinitis and the common cold are the more common indications. Often decongestants are administered as a single drug combined with expectorants.

The two major categories of drugs used as decongestants are the histamine (H_1) receptor antagonists (e.g., dimenhydrinate, diphenhydramine, chlorpheniramine, and hydroxyzine) and the sympathomimetic drugs (i.e., α-adrenergic agonists) (such as ephedrine [EDE], pseudoephedrine [PSE], and phenylephrine [PNE]) (Hendeles, 1993; Johnson and Hricik, 1993; Kanfer et al., 1993). These drugs can be given topically to avoid the systemic effects associated with oral therapy.

Stimulation of α_2-receptors concentrated on precapillary arterioles results in vascular smooth muscle vasoconstriction. Blood flow to the nasal mucosal capillary bed is reduced; excess extracellular fluid associated with congestion and a "runny" nose is thus decreased. α-Receptors are concentrated on the postcapillary venules; when stimulated, the venules act as capacitance vessels that reduce blood volume in the mucosa. Mucosal volume decreases, reducing congestion. Sympathomimetic drugs mimic norepinephrine. Direct-acting agents stimulate one (PNE: α_1) or both types of α-receptors, depending on drug chemistry. Indirect-acting agents (PSE) displace norepinephrine from nerve terminals and sometimes blocks its reuptake, effectively increasing its action on postjunctional α-receptors. Some drugs (e.g., PSE, EDE) are both direct and indirect in their actions. Prolonged use of agents that act indirectly such as EDE may deplete storage granules, and the animal may become refractory to its effects. Alternatively, down-regulation of receptors (tachyphylaxis) may result in refractoriness (Johnson and Hricik, 1993; Kanfer et al., 1993).

Topical agents containing sympathomimetic drugs (i.e., nasal sprays) act within minutes, with minimal side effects. In contrast, rebound hyperemia is common, particularly with extended use of the drugs. The mechanism of rebound hyperemia is not clear but may result from secondary β-adrenergic effects, as β-receptors up-regulate or desensitize α-receptors. Regardless of the cause, repeated contraction of the vasculature can result in ischemia and mucosal damage, perhaps due to loss of nutrition. Oral treatment of sympathomimetic drugs can be associated with a number of adverse reactions. Systemic vasoconstriction may cause hypertension; cardiac stimulation may result in tachycardia or reflex bradycardia. Stimulation of the central nervous system may also prove problematic, particularly with lipid-soluble agonists such as ephedrine. Stimulation of urinary sphincter α-receptors may result in urinary retention. Mydriasis may decrease aqueous humor exit and can prove detrimental in patients with glaucoma. Because of their effects on endocrine and other organs associated with metabolic function, these drugs should be avoided in patients with metabolic disorders, including thyroid disease and diabetes mellitus. There appears to be minimal relationship between plasma drug concentration and nasal decongestant efficacy with the α-agonists, suggesting that topical therapy is as efficacious. In addition, oral administration of some drugs (e.g., PNE) is limited by first-pass metabolism, which prevents therapeutic concentrations of the drug from being reached. Thus, topical therapy may be the preferred route for sympathomimetic drugs. Note, however, that (in the United States) PSE is an "old drug" and as such is exempt from Food and Drug Administration (FDA) regulation, which includes various topical formulations.

Antihistamines are effective for the treatment of allergic rhinitis in human patients. In this scenario, they relieve and prevent itching and rhinorrhea but not nasal "stuffiness." Thus, antihistamines are frequently combined with sympathomimetic drugs. The efficacy of these drugs for the treatment of symptoms related to the common cold (and, presumably, unknown microbial causes in animals) has not been proved. Sedation is the most common side effect of the first-generation antihistamines (diphenhydramine). Newer antihistamines (e.g., chlorpheniramine) are associated with minimal sedation. In contrast to other causes of rhinitis, topic decongestants may be more of a risk for patients with allergic rhinitis because of the risk of drug reaction (rhinitis medicamentosa). This side effect is avoided with topical therapy. Because the antihistamines are safer than the sympathomimetic drugs after oral administration, this may be the preferred route for antihistamines (Hendeles, 1993).

Formulations of topical preparations can influence drug efficacy. Controlled-release polymers can decrease the rate of drug dissolution (and thus its ability to reach cellular targets). Although these differences may not be clinically relevant, it is important to realize that bioequivalency of the topical decongestant products containing older drugs may vary. The major disadvantage of topical agents is their short duration of action.

AEROSOLIZATION AS A ROUTE OF DRUG ADMINISTRATION

The primary indications for aerosolization are to directly deliver drugs to the respiratory tract and to facilitate liquefaction and mobilization of respiratory secretions. The ben-

(e.g., exposure to smoke, cough) are more common than infectious causes. In addition to resolution of the underlying cause, drug therapy should be implemented to control symptoms. Cough can be controlled with peripheral or central antitussives or a combination thereof. Over-the-counter preparations that contain expectorants can prove helpful. Humidifying secretions (liquification of mucoid material) becomes increasingly important with chronic tracheitis and may include nebulization four to six times a day or exposure in a steam-filled bathroom for 15 to 20 minutes three times daily. Physical therapy (coupage) should be implemented after liquifaction of secretions. Short-term therapy with short-acting glucocorticoids may help break the cough cycle, although care must be taken that glucocorticoids do not exacerbate the underlying condition.

Antibiotics are indicated for infectious tracheitis/tracheobronchitis. Infectious tracheobronchitis in dogs (kennel cough) is a complex syndrome caused by multiple organisms, including viruses, bacteria, and mycoplasma. This syndrome is discussed with bronchial diseases.

Structural Disorders of the Trachea

Pharmacologic management of structural disorders of the trachea focuses on supportive therapy.

Hypoplastic Trachea

Slight or moderate tracheal hypoplasia may respond to bronchodilator therapy. Recurrent infections (bacterial) should be anticipated because of a poorly functioning mucociliary tract. Although prophylactic antibiotic therapy is discouraged, antibiotic therapy during active infection should be anticipated. Culture and susceptibility data may be particularly important for these patients because recurrent infections are more likely to occur in them than in animals with a normal trachea. Drugs that facilitate mucociliary clearance should be considered on a daily basis; these might include mucokinetic drugs. More serious episodes of respiratory compromise might benefit from *N*-acetylcysteine therapy administered by any route. The use of bronchodilators should be considered; although the tracheal diameter may not be impacted, the effects of these drugs on peripheral airways can be beneficial. Supportive actions should also include weight control, avoidance of smoke and other environmental contaminants, and avoidance of actions or drugs that cause immune compromise.

Tracheal Collapse

Tracheal collapse as a cause of respiratory distress can progress to a life-threatening situation. Early therapy may help decrease or slow the progression of the syndrome in some animals, simply by decreasing damage to the trachea as a result of paroxysmal coughing. Tracheal rings in afflicted animals lose their ability to remain firm, leading to collapse. The characteristic "goose honk" cough is dry and chronic. Most commonly afflicting smaller breeds, tracheal collapse is often associated with chronic valvular (cardiac) disease, and it is important to differentiate between the two. Diagnosis requires proper radiographic examination and motion studies with either a fluoroscope or a bronchoscope.

Drug therapy targets control of the cough with bronchodilators and centrally acting antitussives. Severe coughs may require narcotic antitussives associated with sedation (a desirable characteristic in some patients) until the cough is controlled. Mucokinetic drugs may also be helpful. Short-term glucocorticoid therapy may be important to minimize the inflammatory response to damage induced by paroxysmal coughing. Nebulization may be helpful, but pretreatment with bronchodilators is probably important. The use of bronchodilators should be considered for their effects on peripheral airways. Bronkoelixir, an old product containing phenobarbital as a sedative and theophylline as a bronchodilator, may prove beneficial. Digitalization reportedly has been beneficial in some patients that do not respond to other therapies (Brayley and Ettinger, 1995). Because tracheal rings are comprised of hyaline cartilage, it is intriguing to consider the possibility of chondroprotectants containing glucosamine and chondroitin sulfates (e.g., Cosequin) in the long-term management of these patients.

Bronchial Diseases

Diagnosis of bronchial diseases should be based on physical examination, thoracic radiography, tracheal or bronchial wash, and bronchoscopy. Examination for structural defects, cytologic studies, and microbial cultures are among the diagnostic tools of use for bronchial diseases.

Canine Infectious Tracheobronchitis

Bordetella bronchiseptica is the bacterial organism most commonly associated with kennel cough. Viral organisms include canine parainfluenza, canine herpes, and canine distemper viruses. The clinical syndrome is characterized by a dry, hacking, paroxysmal cough in an otherwise healthy animal. Clinical signs of this highly contagious syndrome generally appear 3 to 5 days after exposure. Tracheal cytology should reveal neutrophils and bacteria. Therapy of uncomplicated cases is supportive. Antitussives, in relative order of efficacy (least to most), include dextromethorphan (antitussives), butorphanal, and hydrocodone. Hydrocodone may be associated with sedation, which may be beneficial in cases of paroxysmal coughing. Antimicrobial therapy in uncomplicated cases (lasting 7 to 10 days) has not been shown to decrease the time course of the disease; indeed, most antimicrobials used empirically (i.e., amoxicillin) generally do not penetrate bronchial secretions in sufficient quantities to be effective. For the same reason, prophylactic therapy should be used cautiously.

In contrast, antibiotic therapy (in addition to other supportive therapy) is indicated for complicated infections or for dogs whose coughing persists after 2 weeks. Other indicators of complications include any evidence of infection occurring lower than the upper bronchi or systemic signs of illness. Because of the complicated nature, and particularly if the patient has received previous antimicrobials, selection of the appropriate antibiotic should be based on a properly collected culture at the site of infection (not a pharyngeal or laryngeal swab). Selection of an antimicrobial empirically is complicated by the possibility of mycoplasma as a causative agent. Selection of antimicrobials for treatment of respiratory tract infections is discussed in Chapter 10.

Antimicrobials recommended empirically include chloramphenicol, tetracyclines (both include *Mycoplasma* species in their spectrum), and amoxicillin. The latter has decreased the duration of coughing in a field study. Antimicrobial therapy should continue for 2 weeks. Animals that fail to respond to antimicrobial therapy may benefit from the addition of aerosolization with gentamicin (pretreat with bronchodilators).

Because coughing associated with kennel cough can be paroxysmal, a single treatment with a short-acting glucocorticoid might be considered to ameliorate some of the effects of inflammation. In the immunocompromised animal, however, this may lead to spread of infection.

Feline Bronchial Diseases

Feline bronchial diseases include feline bronchial asthma as well as acute and chronic bronchitis and emphysema. Causes of feline bronchial diseases have not been found, but a type I hypersensitivity reaction has been suspected as a cause of asthma. Initial contact between the allergen and bronchial mucosa may lead to the release of histamine and other mediators that allow penetration of the allergen into the submucosa. The resultant inflammatory response to the allergen leads to the characteristic disease. The source of inflammatory mediators includes essentially any cell of the respiratory tract, white blood cells, and platelets. Smooth muscle hypertrophy and increased mucus and inflammatory cell infiltrate (particularly eosinophils) characterize asthma and its clinical signs. Acute bronchitis is generally reversible and short in duration but can be life threatening. Should airway inflammation persist, bronchitis may become chronic. Two to 3 months of inflammation can lead to deposition of fibrous tissue; these lesions tend to be irreversible. Emphysema can occur as a result of chronic bronchitis and is characterized by enlarged airspaces with destruction of bronchiolar and alveolar walls and airway collapse. Cough is the most consistent clinical sign of bronchial disease in cats. Respiratory distress may be absent or episodic, particularly in the presence of bronchial asthma.

Diagnosis should be based on thoracic radiographs; a complete blood count (which may reveal eosinophilia); tracheal or bronchial wash (particularly if bacterial or parasitic causes are suspected); and fecal examination (for parasitic causes). Cultures of *Mycoplasma* species should be performed whenever possible, particularly in nonresponders. Treatment should include environmental management. In particular, exposure to smoke (cigarette, fireplace, or otherwise) should be avoided; other potential environmental allergens include litter dust, perfumes, household cleaning products, deodorants, and insulation products.

Acute respiratory distress due to bronchial disease should be handled as a medical emergency. Administration of drugs should be accompanied by oxygen therapy and rest.

Glucocorticoids are recommended by some authors as initial therapy; however, the lag time to effect may lead to the additional use of bronchodilators as a prudent initial choice. β_2-Adrenergic agonists are preferred (although doses have not been well established for animals), but nonselective agonists can be equally as effective in critical cases. Parenteral rather than oral administration will ensure the most rapid onset of action. Note that epinephrine has marked β_1 (and α) effects and in the presence of hypoxemia can cause fatal cardiac arrhythmias. Aerosolization should not replace, but can be used in concert with, parenteral administration if the stress of aerosolization is not dangerous to severely dyspneic animals. Subcutaneous epinephrine can be administered at presentation and, if the patient responds, repeated every 30 minutes for several doses (Bauer, 1986). Terbutaline can also be administered subcutaneously either in lieu of epinephrine or for animals that fail to respond to epinephrine. Aminophylline can be infused intravenously (2 to 5 mg/kg in 5% dextrose or saline) in animals that fail to respond to β-agonists (Bauer, 1986). The addition of atropine or glycopyrrolate may facilitate bronchodilation. Exacerbation of hypoxia is a complication of bronchodilator therapy due to drug-induced pulmonary vasodilation, and the potential for ventilation-perfusion mismatching necessitates administration of humidified oxygen, particularly with theophylline.

Glucocorticoid therapy should be initiated in conjunction with bronchodilators in cats with bronchial asthma. The permissive effects of glucocorticoids are likely to improve response to bronchodilator therapy. Rapidly acting drugs such as prednisone sodium succinate should be administered at presentation and again at 4 to 6 hours (Bauer, 1986; Moise and Spaulding, 1981). Alternatively, dexamethasone or dexamethasone phosphate may be administered because of its anti-inflammatory potency. The hydration status of the patient should be assessed at presentation and corrected if indicated. Overzealous fluid therapy can prove detrimental, however, and should be avoided. Oral bronchodilator and glucocorticoid therapy can begin when the patient is stabilized.

Response to glucocorticoids in the acute management of respiratory distress in cats may indicate a favorable response to long-term management. If glucocorticoids are used chronically, prednisolone (or prednisone) is the most commonly preferred maintenance drug, although triamcinolone is acceptable. Initially, doses should be as high as 2 to 3 mg/kg divided two to three times a day. A 2- to 3-week trial may be indicated to establish efficacy and need. Maintenance doses are likely to markedly vary among animals and should be slowly tapered to a minimum effective dose 1 to 2 weeks after therapy is started. Doses as little as 1.25 mg/cat every 72 hours may be sufficient in some animals. Glucocorticoid therapy should be maintained for a minimum of 2 months; complete cessation of therapy may not be possible in selected cases. Therapy should be continued for several weeks after cessation of signs to resolve residual and clinically inapparent small airway disease. Tracheal cytology may be helpful in identifying the continued need for anti-inflammatory therapy both before and after therapy is discontinued.

Repositol forms of glucocorticoids should be avoided because of the risk of exacerbation of disease (Bauer, 1986). Remission of clinical signs appears to be more difficult in animals that have received these drugs. For animals for which daily glucocorticoids cannot be given consistently, however, doses of 2 to 4 mg/kg can be given every 10 to 30 days to control clinical signs. In cases of exacerbation in patients receiving glucocorticoids, intermittent high doses of intravenously administered or aerosolized glucocorticoids, and particularly beclomethasone dipropionate, in conjunction with oral maintenance glucocorticoids can be used to treat animals whose disease exacerbates (Bauer, 1986). Alternatively, megestrol acetate has been recommended in lieu of intermittent high doses of glucocorticoids in cats with refractory bronchial asthma (Bauer, 1986).

Addition of bronchodilator therapy should be considered for animals that do not respond sufficiently to glucocorticoid therapy. Intermittent use may help during periods of exacerbation of disease, although long-term therapy may be necessary for some animals. Bronchodilators may decrease the amount of glucocorticoids necessary to control clinical signs. Oral theophylline is the bronchodilator most commonly used for long-term bronchodilator therapy in dogs and cats (Bauer, 1986; Moise and Spaulding, 1981), although terbutaline can be used as an alternative, particularly in animals refractory to theophylline. Alternating between theophylline and β-agonists may prevent the incidence of refractoriness due to down-regulation of β-receptors. Monitoring serum theophylline concentrations is encouraged, particularly in animals that do not respond sufficiently or in animals receiving long-acting theophylline products. Theophylline, particularly long-acting products, might be given to cats in the evening to maximize therapeutic efficacy.

The use of cyproheptidine and leukotriene receptor antagonists as anti-inflammatories should be considered in cats that have not sufficiently responded to or cannot tolerate glucocorticoid or bronchodilator therapy.

Canine Bronchitis

Acute bronchitis is not as likely to present as a life-threatening situation in dogs and refers primarily to duration of clinical signs (Hawkins, 1995). Inflammation that persists more than 2 months may cause permanent damage to airways and is referred to as *chronic bronchitis. Bronchiectasis* refers to irreversible dilation of the bronchi and can be a sequela of chronic bronchitis (inflammation) that does not resolve. Among the causes of bronchitis in dogs are allergies, inhaled irritants, viral, microbial or parasitic infections, and heartworm disease (see Chapter 30). Foreign bodies are a less common cause. As with cats, eradication of the underlying cause is paramount to therapeutic success. Diagnostic aids are the same as discussed for cats. Medical management of chronic airway disease in dogs should be accompanied by weight loss and physical therapy (mild excercise or coupage to facilitate movement of respiratory secretions).

Allergic bronchitis is not a common or easy diagnosis in dogs. The canine respiratory tract is probably more resistant to antigenic stimulation as a cause of cough compared with cats (and people). Parasitic infections including heartworm disease must be ruled out. If airways cytology is supportive of an allergic response and the underlying cause has not been identified or yet eradicated, glucocorticoids are indicated. A minimum effective dose should be rapidly established. Long-term glucocorticoid therapy may not be indicated for dogs unless the disease is associated with eosinophilic or mononuclear infiltrates; this is particularly true for patients with bronchiectasis.

Medical management of chronic bronchitis in dogs must be modified for the individual patient. Obviously, exposure to irritants such as cigarette smoke must be avoided. Bronchodilator therapy provides the mainstay of medical management of chronic bronchitis in many dogs. Drugs used for cats can be used for dogs; the major difference is in frequency of administration, which will be more common in dogs. Night-time (rather than day time) administration of short-acting theophylline products is not indicated for dogs. Therapeutic monitoring is encouraged, particularly for dogs that do not sufficiently respond. Both terbutaline and albuterol can be used for dogs and might be considered in combination with theophylline for nonresponders for which therapeutic concentrations of theophylline have been maximized or on an alternate basis with theophylline.

Control of inflammation may be facilitated by the use of *N*-acetylcysteine; additionally, its expectorant and mucolytic effects also should prove beneficial. Leukotriene receptor antagonists should be considered as well. Glucocorticoids should be used only if cytologic examination indicates a large mononuclear or predominantly eosinophilic component to the inflammation. The routine use of antimicrobials for the treatment of chronic diseases is controversial. Distinction between infection and colonization should be made whenever possible. Selection of the antimicrobial should be based on culture and susceptibility data. Cytologic findings should be used to guide the need for antimicrobial therapy; culture data are likely to enhance therapeutic success. Antimicrobial therapy should target *Bordetella*. The potential of infection with *Mycoplasma* should not be overlooked. A trial course of antimicrobials is indicated if cytologic findings are supportive of microbial infection; care should be taken to use an antimicrobial effective against *Mycoplasma* before microbial infection is ruled out. More in-depth discussion of antimicrobial therapy for respiratory tract infections can be found in Chapter 10.

The role of antitussives in the treatment of diseases depends on the character of the cough. Inflammation and infection can result in mediator release and cough without an increase in bronchial secretions. Antitussives are generally indicated if the cough is nonproductive. In the case of productive cough, the use of expectorants or mucolytics may actually exacerbate cough. Hydration of respiratory secretions is critical to effective mucociliary transport function. As such, diuretics are contraindicated, and daily water intake must be maintained. Exposure to humidified air (i.e., humidifiers, vaporizers, or a visit to the bathroom during family member showers) is likely to facilitate liquefaction of respiratory secretions.

Pulmonary Diseases

As with other regions of the respiratory tract, causes of pulmonary disease include viral, microbial, and parasitic infections, allergic (hypersensitivity) or immune-mediated

Granulomatosis, whether eosinophilic or lymphoid, is accompanied by a poor prognosis. Combination therapy should include cyclophosphamide (50 mg/m^2 orally every 48 hours) and immunosuppressive doses (1 mg/kg every 12 hours) of prednisone. *N*-acetylcysteine and bronchodilators should be used as previously discussed.

Vascular Diseases

Pulmonary Hypertension

Pulmonary hypertension is most commonly a secondary problem, and, as such, treatment should focus on eradication of the underlying cause. Causes can be precapillary (alveolar hypoxia caused by lung disease or high altitude) or postcapillary (congenital heart disease with left to right shunting of blood or acquired heart disease). Dirofilariasis is probably the most common cause of pulmonary hypertension in dogs; bronchial asthma might be a cause in cats. Currently, no drugs have been found that can be used in the clinical environment to cause pulmonary arterial dilation while avoiding systemic arterial vasodilation. Hence, use of pulmonary vasodilators is generally accompanied by undesirable systemic hypotension and tachycardia.

Pulmonary Edema

As in any tissue, excessive fluid accumulation in the lungs occurs as a result of increased hydrostatic pressure, decreased oncotic pressure, lymphatic blockage, or changes in vascular permeability. Increased hydrostatic pressure generally occurs as a result of volume (vascular) overload. In contrast to fluid dynamics in other tissues, hydrostatic pressure in the lungs is low, and lymphatic flow is high. Expansion of lymphatics, as well as fluid movement into the alveoli, can accommodate marked increases in capillary pressure. Thus, capillary hydrostatic pressures must markedly increase for excessive fluid to accumulate in the lungs. Hypoalbuminemia is not a likely cause of pulmonary edema. Rather, vascular overload as a result of overcirculation is a common cause of pulmonary edema secondary to increased oncotic pressure. Left heart failure is the most common cause of vascular overload. Regardless of the cause of pulmonary edema, oxygen therapy and actions that minimize stress and anxiety of the patient are indicated. Unless contraindicated, bronchodilators should be administered.

Diuretics are indicated for treatment of pulmonary edema associated with volume overload. Drugs that cause sodium and chloride excretion (i.e., furosemide) may be more effective, particularly in cases of sodium and water retention. Diuretics are contraindicated for patients that are hypovolemic. Use in normovolemic animals should be cautious and the dose titrated to the minimum needed to control clinical signs associated with pulmonary edema. In life-threatening situations of pulmonary edema associated with volume overload, venous dilators can be used to increase the capacitance of the vascular system, thus "drawing" the increased volume into the veins, away from the heart and pulmonary system. Topically applied nitroglycerin or morphine sulfate (0.1 mg/kg intravenously as needed) can be used for this purpose. Morphine has the added advantage of sedating animals whose anxiety is contributing to hypoxia. Methylxanthines such as theophylline might be helpful in the short term because they also bronchodilate, and in the patient with heart failure they may improve contractility. They will also, however, increase oxygen demand by the heart, and their diuretic effects are short lived (2 to 3 days).

Pulmonary edema as a result of increased vascular permeability probably occurs more frequently than is anticipated. Any disorder that causes inflammation of the lungs will contribute to pulmonary edema of the lungs. The extreme manifestation of permeability-induced pulmonary edema is the acute respiratory distress syndrome described in humans. The fluid contains protein that, as long as it is present, will continue to provide oncotic draw of fluid into the parenchyma. Pulmonary edema of this type is difficult to treat. Pulmonary wedge pressure is normal; vascular overload is not present. In this situation, diuretics will serve to decrease fluid retention only at the cost of extracellular fluid volume and thus are not an effective treatment. Glucocorticoids might be indicated to decrease inflammation and support bronchodilation, although their use is controversial. Among the glucocorticoids, methylprednisolone should be considered because of its ability to scavenge oxygen radicals. Vasodilators might be used; the therapeutic intent of these drugs is not certain, but decreased delivery of blood to the lungs and a further decrease in wedge pressure may decrease movement of blood into the parenchyma. Vascular shunting and hypotension may, however, preclude their use. Newer therapies are likely to target mediators responsible for permeability, such as tumor necrosis factor or nitric oxide, or replace surfactant.

Miscellaneous

Aspiration Pneumonia

Clinical signs resulting from aspiration pneumonia may result from mechanical obstruction in small or large airways, an inflammatory response to foreign materials (including gastric acid or other chemicals), or bacterial infection. Decreased pulmonary compliance and bronchoconstriction are likely to be a source of some of the clinical signs. Oxygen therapy, bronchodilatory therapy, and positive-pressure ventilation are indicated, the latter particularly for patients with poor pulmonary compliance. Bronchoscopy can be used to guide removal of visible foreign material. Glucocorticoids might be used to minimize the inflammatory response during the initial phase of therapy; methylprednisolone and an *N*-acetylcysteine might be considered to minimize oxygen radical damage. Immune suppression probably negates the advantages of controlled inflammation after 48 hours of therapy. Routine antibiotic coverage is controversial; antibiotic therapy might be more appropriately held until evidence of infection exists.

Near Drowning

Standard supportive therapy for near drowning includes oxygen, positive-pressure ventilation, and therapy for shock. Bronchodilators may be of benefit. Use of glucocorticoids is controversial; however, use of methylprednisolone is appealing because of its oxygen scavenging abilities. *N*-acetylcysteine therapy may be useful for its oxygen radical scavenging effects as well as other benefits. Short-term therapy may be of benefit. Use of antimicrobials should probably be reserved for evidence of infection. Supportive therapy should also target the advent of cerebral edema; an additional advantage of using methylprednisolone is minimizing oxygen radical damage in the event of cerebral hypoxia.

Smoke Inhalation

Oxygen therapy is critical for removal of carbon monoxide; the half-life of carboxyhemoglobin reduces from 4 to 0.5 hours in the presence of 100% oxygen. Other supportive therapy includes airway hydration (as needed), bronchodilators, and, if indicated, positive-pressure ventilation. Short-term administration of glucocorticoids (methylprednisolone preferred) may be of benefit to minimize inflammation and oxygen radical damage and to facilitate bronchodilation.

Diseases of the Pleura

A number of diseases are associated with pleural effusion, and successful management of the effusion largely depends on resolution of the underlying diseases (Bauer and Woodfield, 1995). Thus, pleural effusion due to cardiac failure, neoplastic disease, and other causes are treated by treatment of the cause; pleurodesis is used as needed to management life-threatening effusion. Pleurodesis stimulated by lavage of irritating substances (with the intent of "closing" the pleural space by causing fibrosis) is strongly discouraged. An exception is made for empyema, which can be a primary disease.

Empyema

Empyema refers to the accumulation of infectious inflammatory material within the pleural space. Infection can be an extension of a primary pulmonary lesion, the result of direct penetrating trauma, or of a lymphatic or hematogenous route. Accumulation of inflammatory debris provides a continued colloidal draw of fluid into the cavity. Lymphatic obstruction by debris further worsens the ability of pleural fluid mechanics to resolve the accumulation. Thus, chest drainage is critical to successful control. Microbiologic examination (including Gram stains initially pending culture and susceptibility data) should be the basis of initial antimicrobial selection. Subsequent daily cytologic studies with Gram staining should provide the basis for response to therapy. The fluid should be recultured if bacterial growth has not changed for 2 to 3 subsequent days or if the organism's morphology changes. Note that absence of an organism on Gram stain does not necessarily indicate the absence of organisms at the site of infection. Because the incidence of anaerobic infections in empyema is high in both dogs and cats, both aerobic and anaerobic cultures should be collected. Care must be taken to properly collect the anaerobic culture. Despite the presence of organisms on Gram stains, cultures often do not yield growth. Thus, antimicrobial therapy often must be empirical.

Empirical therapy should include drugs effective against anerobic organisms. Although ampicillin has been recommended previously as the drug of choice, resistance to this organism is increasing. Thus, unless culture and susceptibility data are available to direct otherwise, the amoxicillin/clavulanic acid combination is recommended. In addition to improved efficacy, this drug is more orally bioavailable than is amoxicillin, and can be given less frequently. Despite these favorable characteristics, however, double dosing at 8-hour intervals is recommended for treatment of empyema with amoxicillin/clavulanic acid.

Clindamycin is recommended for treatment of empyema in cats but could also be considered for dogs. Clindamycin is effective against most anaerobes, including *Nocardia* species. In severe infections, the aminoglycoside amikacin is very effective against *Nocardia* (once daily therapy); note, however, that the aminoglycosides are not effective against other anaerobic organisms. In the event of a gram-negative organism, combination therapy is recommended. Both clindamycin and amoxicillin/clavulanic acid can be combined with a number of drugs effective against gram-negative organisms, including amikacin or enrofloxacin.

Because of their excellent tissue penetrability and their efficacy against *Nocardia* and *Actinomycetes* species, trimethoprim-sulfonamide (sulfadiazine preferred) has been used for treatment of empyema. Resistance may be a limiting factor; combination with an effective penicillin will enhance drug delivery to *Nocardia,* potentially resulting in synergistic action. As with the penicillins, double doses are recommended for the sulfonamides. Because therapy is likely to be prolonged to several months, clinical signs of immune-mediated reactions to the sulfonamides should be anticipated and the drug discontinued if detected.

The use of pleural lavage as supportive therapy is controversial. Certainly lavage is more indicated in the initial stages of therapy to remove inflammatory debris that might be blocking lymphatic or other drainage pathways. Addition of heparin may help reduce fibrin formation as well as potentiate phagocytosis of the debris by macrophages. Use of proteolytic enzymes in lavage fluid is unsupported.

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32 Drug Therapy for Endocrinopathies

Dawn Merton Boothe

- INTRODUCTION
- THYROID GLAND
- Synthesis
- Hypothyroidism
  - Pathophysiology
  - Baseline and Provocative Testing of Thyroid Status
  - Therapy of Hypothyroidism
  - Response to Therapy
- Hyperthyroidism
  - Pathophysiology
  - Baseline and Provocative Testing
  - Drugs Used To Control Hyperthyroidism
  - Drugs Used To Cure Hyperthyroidism
  - Drugs Used To Control Clinical Signs of Hyperthyroidism
- DISEASE OF THE PARATHYROID GLAND
- Abnormal Calcium Homeostasis
- Hypoparathyroidism
- Hyperparathyroidism (Hypercalcemia)
- Therapy of Hypercalcemia
- Secondary Hyperparathyroidism
- DISEASE OF THE PANCREAS: DIABETES MELLITUS
- Normal Physiology
- Provocative Testing
- Drug Therapy
  - Insulin preparations
  - Insulin Therapy
  - Complications of Insulin Therapy
- DISEASES OF THE ADRENAL GLANDS
- Hyperadrenocorticism
  - Pathophysiology
  - Baseline and Provocative Testing
  - Therapy
- Hypoadrenocorticism
  - Pathophysiology
  - Diagnosis
  - Therapy
- DISORDERS OF THE PITUITARY GLAND
- Disorders of Growth Hormone
  - Pathophysiology
  - Diagnostics: Provocative Testing
  - Therapy
- Diabetes Insipidus
  - Provocative Testing with DDAVP
  - Therapy

Hormones are either protein (e.g., insulin, glucagon, and thyroid hormones) or steroidal (e.g., glucocorticoids, mineralocorticoids, and reproductive hormones) in structure. The cellular effects of hormones are achieved (generally) either through interactions with cell membrane receptors (thus stimulating a cascade of intracellular reactions, often involving secondary messenger systems) or through passive diffusion to the cellular nucleus, stimulation of protein synthesis, and subsequent formation of the effector protein. Generally, but not always, protein hormones interact with cell membrane receptors (an exception being thyroid hormones), whereas steroidal hormones passively diffuse through the cell membrane to the nucleus.

Drug therapy for the endocrine systems is implemented for one of three reasons: to replace a hormone deficiency; to prevent or reduce the formation or effects of an overactive hormone; or to provocatively test for the presence of an endocrine disease. Understanding the proper uses of the drugs depends on an appreciation of the normal physiology of each endocrine system, including mechanisms of control and behavior of target tissues (Tables 32–1 and 32–2).

THYROID GLAND

Synthesis

Iodine is actively accumulated by an active transport process in the follicular cells of the thyroid gland (Fig. 32–1). Iodine passes down an electrochemical gradient. Once in the follicular lumen, iodine is oxidized and subsequently inserted into a thyroglobulin amino acid, tyrosine. Thyroid peroxidase is the enzyme responsible for oxidation and insertion. At the same time, thyroglobulin is synthesized by the endoplasmic reticulum and Golgi apparatus and released in vesicles into the lumen. The monoiodinated form results from the initial iodination of tyrosine; mono products are then joined to form di-iodinated molecules; combinations yield the triiodinated tyrosine, triiodothyronine (T_3), and thyroxine (T_4) (Fig. 32–2). Thyroid peroxidase mediates the formation of mono- and di-iodinated tyrosine residues as well as the formation of T_3 and T_4 from these residues. Four or more sites exist in the thyroglobulin molecule for the generation of thyroid hormones; generally each molecule contains three to four residues of T_4 and zero to one residue of T_3 (humans). The preformed hormones are released from the colloid of the follicular cells upon stimulation with thyroid-stimulating hormone; much greater quantities of T_4 are released than are T_3. The hormones are transported to the target cell, bound to one of several transport proteins. At the target cell, both hormones are taken up. T_4 is converted to T_3, however, which causes physiologic effects. Thyroxine (T_4) is deiodinated on the outer ring to produce T_3. However, deiodination of the inner rig produces reverse T_3 (rT_3), which is physiologically inactive (Dunn, 1995). Thyroid hormones stimulate many metabolic processes, including the activity of many enzymes, metabolism of vitamins and minerals, the regulation of other hormones, and stimulation of calorigenesis, protein and enzyme synthesis, and carbohydrate and lipid metabolism. They also have marked inotropic and chronotropic cardiac effects, stimulate erythropoiesis, and affect virtually every body tissue.

Hypothyroidism

Pathophysiology

Primary hypothyroidism is a disorder that afflicts principally dogs. Causes include lymphocytic thyroiditis, idio-

Table 32–1. Concentrations of Various Hormones in Normal Dogs and Cats

- Cortisol
  - 0.5–6.0 µg/dL (D)
  - 1.0–4.4 µg/dL (mean 2.9 µg/dL) (C)
  - Post-ACTH
    - 6–17 µg/dL (D)
    - 9.8–11.1 µg/dL (at 15 and 30 min post-ACTH, respectively) (C)
  - ACTH <20 pg/mL (>40 pg/mL consistent with PDH hyperadrenocorticism) (D, C)
- Growth hormone
  - <5 ng/mL (D)
- Thyroid hormones
  - T$_4$
    - 13–36 ng/mL (D)
    - 9–40 ng/mL (C)
  - FT$_4$
    - 0.0028–0.017 ng/mL (47 euthyroid, mean ± SD 0.006 ± 0.003 ng/mL; 29 hypothyroid dogs, 0.0017 ± 0.0018 ng/mL)
    - 8–18 pg/mL
  - T$_3$
    - 0.8–1.5 ng/mL (D)
    - 0.7–1.1 ng/mL (C)
  - FT$_3$
    - 2.5–6.0 pg/mL (D)
  - FT$_3$
    - 0.06–0.58 ng/mL (C)
  - TSH
    - 2.7–7.9 ng/mL (range in 17 euthyroid dogs)

Abbreviations: ACTH = adrenocorticotropic hormone; C = cat; D = dog; FT$_3$ = free triiodothyronine; FT$_4$ = free thyroxine; PDH = pituitary dependent hyperadrenocorticism; T$_3$ = reverse triiodothyronine; T$_3$ = triiodothyronine; T$_4$ = thyroxine; TSH = thyrotropin = releasing hormone.

pathic atrophy, and neoplastic destruction (Feldman and Nelson, 1996). Secondary hypothyroidism results from a deficiency of thyrotropin-stimulating hormone (TSH) secreted from the pituitary gland. Tertiary hypothyroidism results from a lack of hypothalamic thyrotropin-releasing hormone (TRH) and its subsequent effects on TSH. Congenital absence of the thyroid glands and iodine deficiency are rarer causes of hypothyroidism. Cats suffering from clinically evident hypothyroidism generally develop the disorder in response to iatrogenic removal or destruction of thyroid tissue as part of the treatment for hyperthyroidism. Iodine deficiency is a much rarer cause of hypothyroidism in kittens.

The clinical signs of hypothyroidism refer to multiple body systems. Dermatologic signs include unilateral or bilateral nonpruritic alopecia that can be localized or diffuse. The hair coat is dry, course, and slow to grow. Hyperkeratosis, scaling, dandruff, or seborrhea may be present. Immunosuppression may lead to secondary pyoderma. Cardiac abnormalities may develop with severe hypothyroidism, including bradycardia and reversible cardiomyopathy. Reproductive disorders that may develop include abnormal estrous cycles, infertility, and lack of libido. Neuromuscular dysfunctions include weakness or stiffness, muscle wasting, neuropathies, and weakness of facial muscles. Seizures may be worsened in the epileptic patient with hypothyroidism. Diarrhea is the most common gastrointestinal manifestation of hypothyroidism. In cats, lethargy and obesity are the most common clinical manifestations of hypothyroidism. Clinical laboratory abnormalities include normocytic, normochromic, nonregenerative anemia with leptocytes on the hemogram; pure red cell aplasia; and hypercholesterolemia with hypertriglyceridemia or hyperlipidemia.

Baseline and Provocative Testing of Thyroid Status

Concentrations of circulating thyroid hormones are the basis of diagnosing hypothyroidism. Basal hormone concentrations are easily influenced by a number of uncontrollable factors; thus, thyroid hormones are ideally measured after stimulation with exogenous TSH or TRH (Beale, 1990). Thyroxine (T$_4$) is the primary hormone secreted from the thyroid gland; however, its metabolic product triiodothyronine (T$_3$) is the physiologically active hormone. Only 40% of T$_3$ in the blood is secreted from the thyroid. Most T$_3$ results from metabolism or conversion of T$_4$ by peripheral tissues to T$_3$ and reverse T$_3$ (rT$_3$). Thus, most body T$_3$ is located inside cells at the site of conversion. As a result, plasma concentrations of T$_3$ do not necessarily reflect total body T$_3$, and T$_4$ concentration is the principal hormone tested.

Thyroid hormones are bound to plasma proteins. Only a very small fraction of circulating hormones is unbound and thus physiologically active. Most laboratories measure total (bound and unbound) T$_3$ and T$_4$ concentrations. Measurement of unbound hormone may more accurately reflect the status of the thyroid axis. Tests for the free fraction of thyroxine (FT$_4$) are increasingly being offered by diagnostic laboratories (Ferguson, 1996). A number of techniques have been developed to quantitate the fraction of unbound thyroxine. Included are equilibrium dialysis, which serves as the gold standard for comparison with other methods, and several immunoassays that indirectly detect FT$_4$. Currently, methods that depend on equilibrium dialysis appear to offer the most accurate measurements of T$_4$. Regardless of the test, normal thyroid hormone concentrations will vary with the laboratory and the kit; the test must be validated for the target species (i.e., dog or cat).

Occasionally, T$_3$ concentrations may be of some diagnostic benefit in the hypothyroid patient. Thyronine concentrations should be measured in patients for which a conversion defect (T$_4$ to T$_3$) is suspected. In such patients, even if receiving thyroxine supplementation, basal concentrations of T$_3$ may be low, and T$_4$ concentrations will be normal to high. The occasional animal may actually convert T$_4$ to T$_3$ at a very high rate. Phenobarbital and other drugs that induce enzymes may increase the metabolism of thyroid hormones and may cause decreases in either or both T$_3$ and T$_4$. When combined with T$_4$ and T$_3$, rT$_3$ (which should approximate one-fourth to one-half of the T$_3$ concentration) may help differentiate hypothyroid from euthyroid animals whose T$_3$ and T$_4$ concentrations are falsely decreased.

The TSH stimulation test has not proved useful in the diagnosis of hypothyroidism in cats but is useful for dogs. Bovine TSH is used as the provocative agent. The dose and testing time vary (Feldman and Nelson, 1996), but generally T$_4$ concentrations are measured 4 to 8 hours after administration. Although the responsiveness of the thyroid gland to TSH depends on the duration of disease and severity of thyroid gland atrophy, the hypothyroid animal

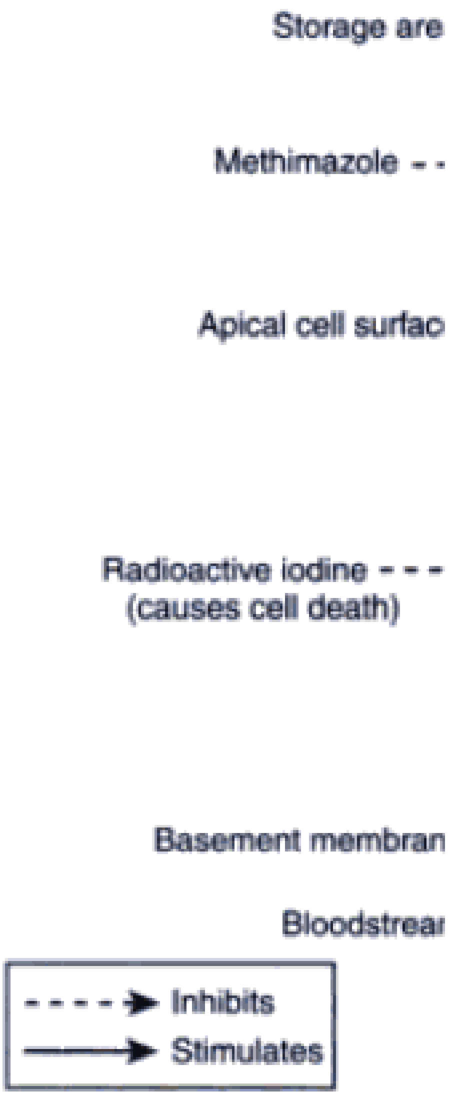

Figure 32–1. Synthesis of thyroid hormones. Iodine is concentrated in the apical cell colloid. At the same time, thyroglobulin is synthesized by the smooth endoplasmic reticulum and Golgi apparatus. At the apical cell surface, thyroglobulin and then tyrosine are iodinated, iodotyrosyl precursors are coupled to form thyronine and thyroxine, and all are stored in colloid. Thyroxine peroxidase mediates iodinization of the thyroglobulin-iodotyrosyl complexes. When signaled by thyroid-stimulating hormone (TSH), thyroglobulin (as a colloid droplet) is engulfed by pinocytosis into the apical cell. Lysosomal degradation releases thyroxine and thyronine, which enter the blood stream, and the iodotyrosyl precursors, from which iodine is released and recirculated. The thyroid hormones reach target tissues bound to a circulating protein. Once inside the cell, thyroxine is converted to thyronine, the physiologically active thyroid hormone. Targets of thyroid hormone inhibition include administration of radioactive iodine, which is accumulated in active cells, ultimately leading to their destruction; methimazole, an inhibitor of thyroid peroxidase (controls but does not cure); and control of peripheral tissue response to excessive thyroid hormone release. I = iodine.

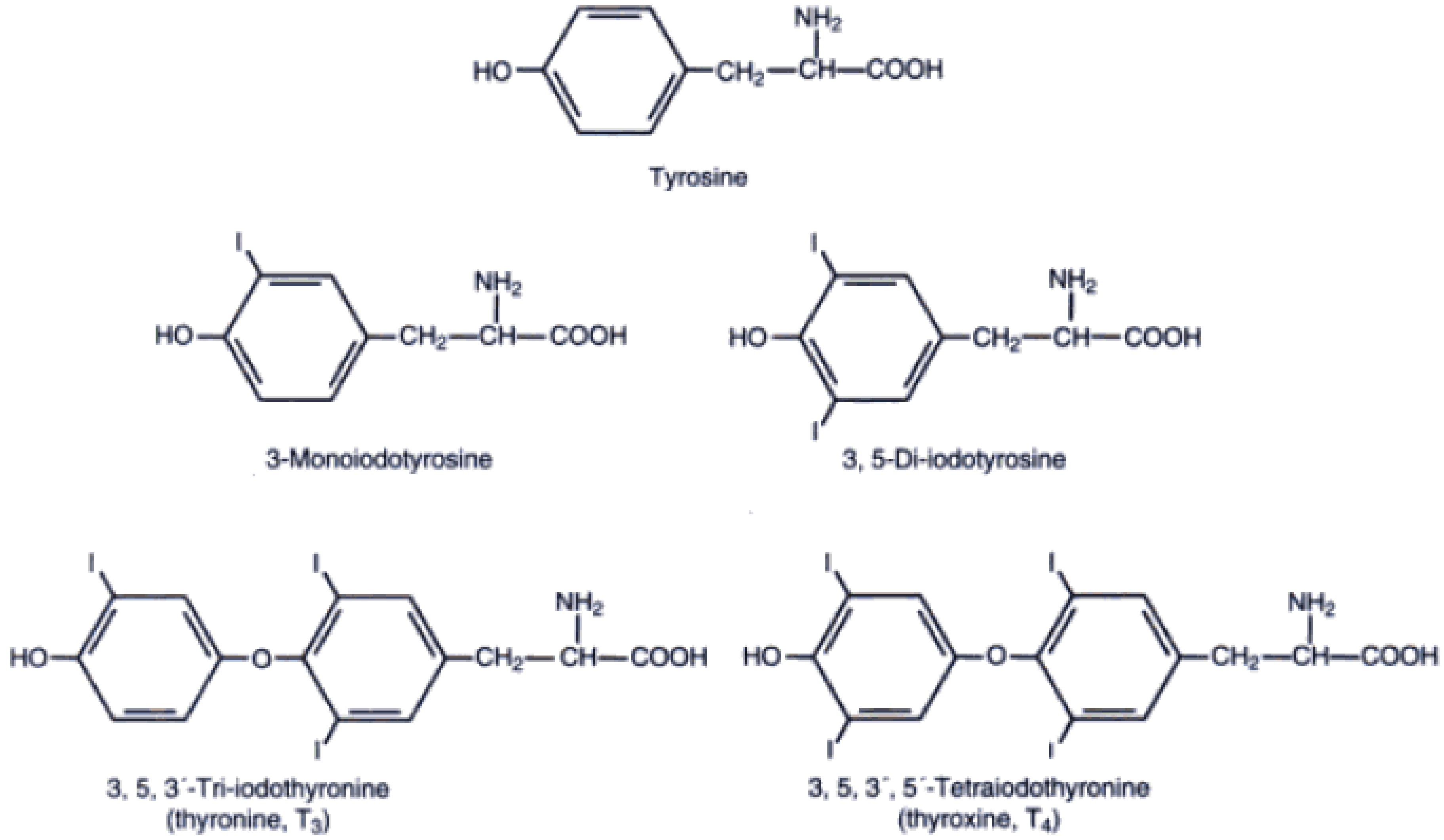

Figure 32–2. Iodination of tyrosine results in the formation of the monoiodinated and di-iodinated precursors. Combinations of the two yield thyroxine (the tri-iodiniated product) and thyroxine. This reaction and the iodination of tyrosine are mediated by thyroid peroxidase.

mones on the heart. Thyrotoxicosis probably increases the responsiveness of the myocardium to the catecholamines by increasing the number of catecholamine receptors.

Baseline and Provocative Testing

Baseline concentrations of either T_3 or T_4 can be used to diagnose hyperthyroidism (Peterson, 1982; Feldman and Nelson, 1996). The diagnosis of hyperthyroidism may require several serial T_4 measurements as the disease progresses if initial concentrations are borderline. The effects of severe nonthyroid disease may mask hyperthyroidism to some degree. Provocative testing can be used to facilitate diagnosis of hyperthyroidism in cats with high normal concentrations. Feedback inhibition of TSH by peripheral hormones is the basis of the T_3 suppression test. Serum T_4 concentrations should be decreased by at least 50% after seven doses (8 hours apart) of T_3 (25 g). Response to TSH also can be used to detect the hyperthyroid animal. Serum T_4 concentrations should increase in response to TSH (1.0 IU/kg IV) in the normal animal (either a twofold increase; or an increase to 40 ng/mL; or an increase of 25 ng/mL above baseline). A greater response should be anticipated in the hyperthyroid animal.

Several radionuclides are concentrated by active follicular cells of the thyroid gland. Uptake of radioactive iodine or pertechnetate can confirm hyperthyroidism as well as delineate functional thyroid tissue, establish the extent of thyroid involvement, and detect metastasis. The radionuclides differ in onset of action, half-life of decay, destruction to surrounding tissue, incorporation into thyroid gland or thyroid hormones, and cost and availability. Radioactive iodine is ultimately incorporated into thyroid hormones as part of the tyrosine groups. In contrast, pertechnetate is not bound to thyroglobulin or stored in the thyroid gland.

Iodine-131 is inexpensive and readily available but has a long decay half-life (8.1 days). Scanning cannot occur until 24 hours after the injection. Both β and γ particles are eliminated by iodine-131, thus increasing total body exposure. Compared with iodine-131, iodine-123 has a shorter half-life (13 hours) and emits no β particles. Although more ideal for scanning, I^{123} is more expensive. Pertechnetate has the shortest half-life (6 hours), and imaging can occur within 20 minutes of injection. Pertechnetate results in the smallest amount of exposure to radiation. Use of radionuclides to treat hyperthyroidism is discussed later.

Drugs Used To Control Hyperthyroidism

Hyperthyroidism may be controlled with methimazole (initially, depending on severity, 10 to 15 mg/day; based on monitoring, 2.5 to 10 mg/cat orally divided every 8 to 12 hours) and propylthiouracil (10 mg/kg or 50 mg/cat orally every 8 to 12 hours) (Feldman and Nelson, 1996; Peterson, 1982). Both can be used as either the sole drug to manage hyperthyroidism or in preparation for surgery. Although both drugs effectively reduce circulating thyroid hormone concentrations to normal levels, the incidence of adverse reactions is higher (20% to 25%) after propylthiouracil therapy (Peterson, 1981, 1984). Side effects include vomiting, anorexia, lethargy, thrombocytopenia, and immune-mediated hemolytic anemia. Both drugs block synthesis of thyroid hormones and, specifically, thyroid peroxidase activity necessary for coupling of tyrosine residues by acting as a preferential substrate for the enzyme. Thyroid hormones (T_3 and T_4) are not secreted. Carbimazole is a methimazole pro-drug currently used in Europe but not available in the United States. It appears to be equal in efficacy and safer than either methimazole or propylthiouracil.

Methimazole appears to be as effective as, and is longer-acting and safer than, propylthiouracil (Thoday and Mooney, 1992; Feldman and Nelson, 1996). Adverse effects occur, however, in up to 15% of cats. The most common side effects of methimazole are anorexia, vomiting, and lethargy. Often, these clinical signs resolve despite continued administration. Several less common side effects might require cessation of therapy. Severe gastrointestinal signs (vomiting and diarrhea) may not resolve. Self-induced excoriations of the face and neck may occur within the first 6 weeks of therapy and may be responsive to glucocorticoid therapy.

Hepatotoxicity is largely reversible and should resolve if the drug is discontinued. Hematologic abnormalities that may not be associated with pathology include eosinophilia, lymphocytosis, and transient leukopenia. In some cases, however, these dyscrasias become severe and clinically significant; in particular, thrombocytopenia and agranulocytosis have been associated with methimazole therapy. The mechanism of hematologic disorders induced by methimazole is not understood. Although the phenomenon is undocumented, cats receiving methimazole may exhibit prolonged bleeding despite normal platelet counts. In human patients receiving propylthiouracil, vitamin K therapy has reduced bleeding caused by hypoprothrombinemia; however, the benefits of vitamin K therapy have not been studied in cats receiving thyroid peroxidase inhibitors (Graves, 1996). Immune-mediated hemolytic anemia, not uncommon with propylthiouracil, does not appear to occur with methimazole. Serum antinuclear antibodies may develop particularly at high doses (15 mg/day) but they are not associated with lupus-like syndrome.

Because many of the side effects of methimazole are dose dependent, the daily dose should be maintained at the lowest effective. Individual variation in methimazole disposition necessitates monitoring serum T_4 levels every 2 to 3 weeks to determine therapeutic efficacy and to guide dosing regimens (Peterson, 1982; Thoday and Mooney, 1992; Feldman and Nelson, 1996). If T_4 concentrations fall to low or low normal, the dose should be decreased by 2.5- to 5-mg increments. If concentrations fail to fall, the dose of methimazole can be increased in 5-mg increments. A complete blood count and platelet count should be measured at 2- to 3-week intervals during induction of therapy. A total dose of 25 to 30 mg/day may be necessary to control thyroid hormone concentrations in some cats. Because adverse reactions can occur at any time, T_4 concentrations should be measured monthly until stabilized and then at 3- to 6-month intervals. Decreased T_4 concentration does not necessarily indicate that the dose of methimazole needs to be decreased. Thyronine concentrations apparently are more able to remain normal than T_4 concentrations during therapy because conversion of T_4 to T_3 is not inhibited. Because methimazole remains in the intrathyroidal

thyroidectomy. One to two drops of a saturated solution of potassium iodide can be administered in gelatin capsules beginning 10 days before surgery.

DISEASES OF THE PARATHYROID GLAND

Abnormal Calcium Homeostasis

The parathyroid glands function in calcium homeostasis and are very sensitive to changes in serum ionized calcium concentrations (Wingard et. al., 1995). Calcium homeostasis is accomplished by the integrated influences of parathyroid hormone (PTH) on calcium and phosphorus reabsorption in the bone and distal renal tubular cell and by the intestinal absorption of calcium mediated by 1,25-dihydroxycholecalciferol (vitamin D) (Fig. 32–3). Hypocalcemia causes increased PTH secretion, which in turn causes increased calcium resorption from urine (distal renal tubule), increased mobilization of calcium and phosphorus from bone, and increased vitamin D synthesis. Parathyroid hormone mediates the conversion of vitamin D to its active form (Fig. 32–4). Serum ionized calcium concentrations normally fluctuate less than 0.1 mg/dL. Renal and, to some degree, bone activities mediate the acute response to calcium homeostasis. Intestinal reabsorption of calcium, which replaces calcium reabsorbed from bone, may take several days to occur, in part because of the time necessary for synthesis or activation of vitamin D (Feldman and Nelson, 1996).

Hypoparathyroidism

Cessation of PTH secretion from the parathyroid glands results in the loss of mobilization of calcium from the bone, the loss of calcium retention in the kidneys, and the loss of absorption from the intestine. The primary clinical manifestation of hypoparathyroidism reflects decreased serum concentrations of calcium. Hypocalcemia and, in particular, decreased concentrations of ionized calcium lead to neuromuscular hyperexcitability. Hyperexcitability occurs as the stabilizing influence of calcium on sodium permeability in the neuronal cell is lost. Although both the central and peripheral nerves are affected, clinical signs of tetany are usually peripheral in nature, ranging from a latent

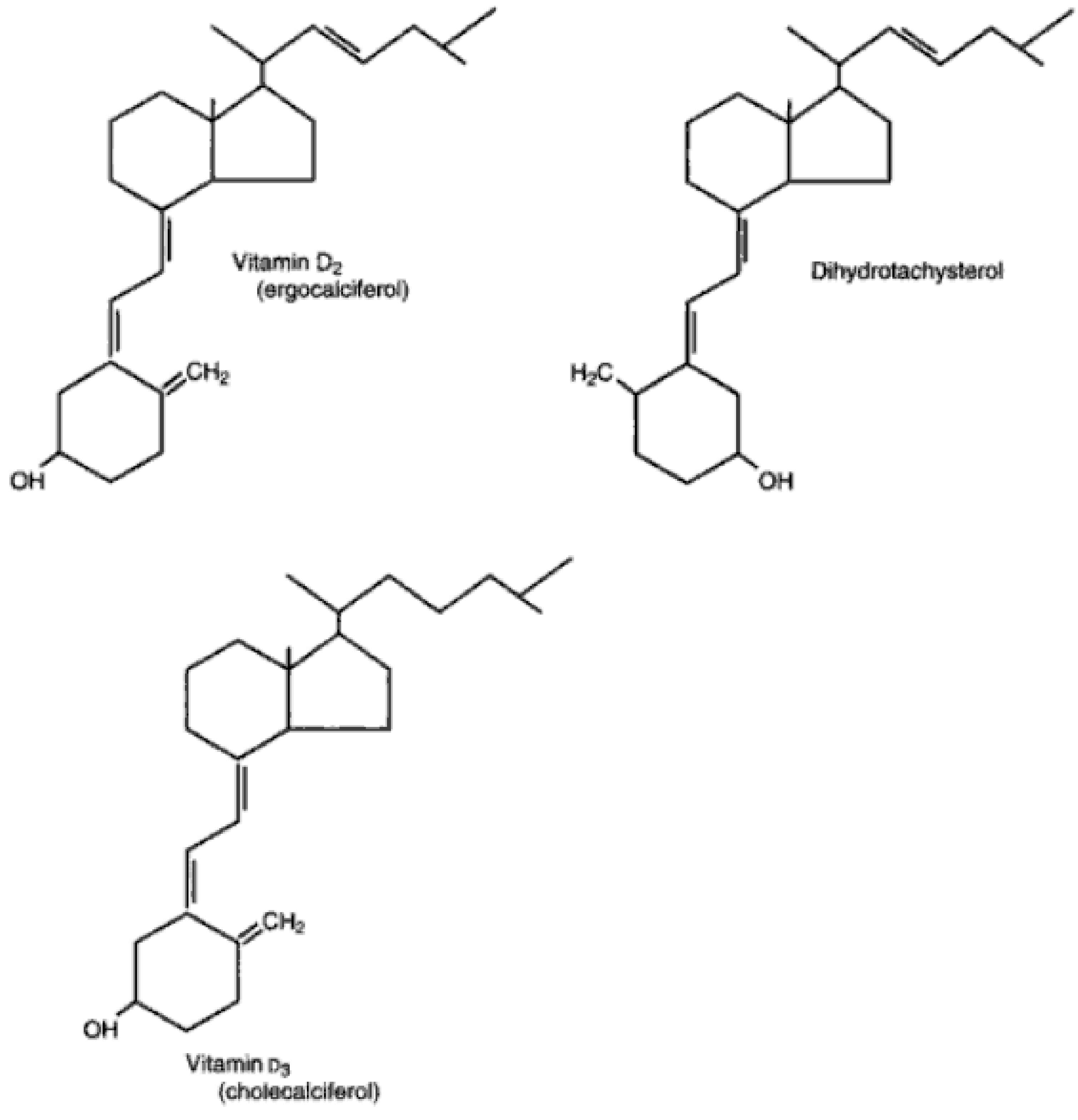

Figure 32–3. Structures of ergocalciferol, vitamin D_2 present in plants, and cholecalciferol, vitamin D_3 present in animals. Dihydrotachysterol is a commercially available congener of vitamin D_2.

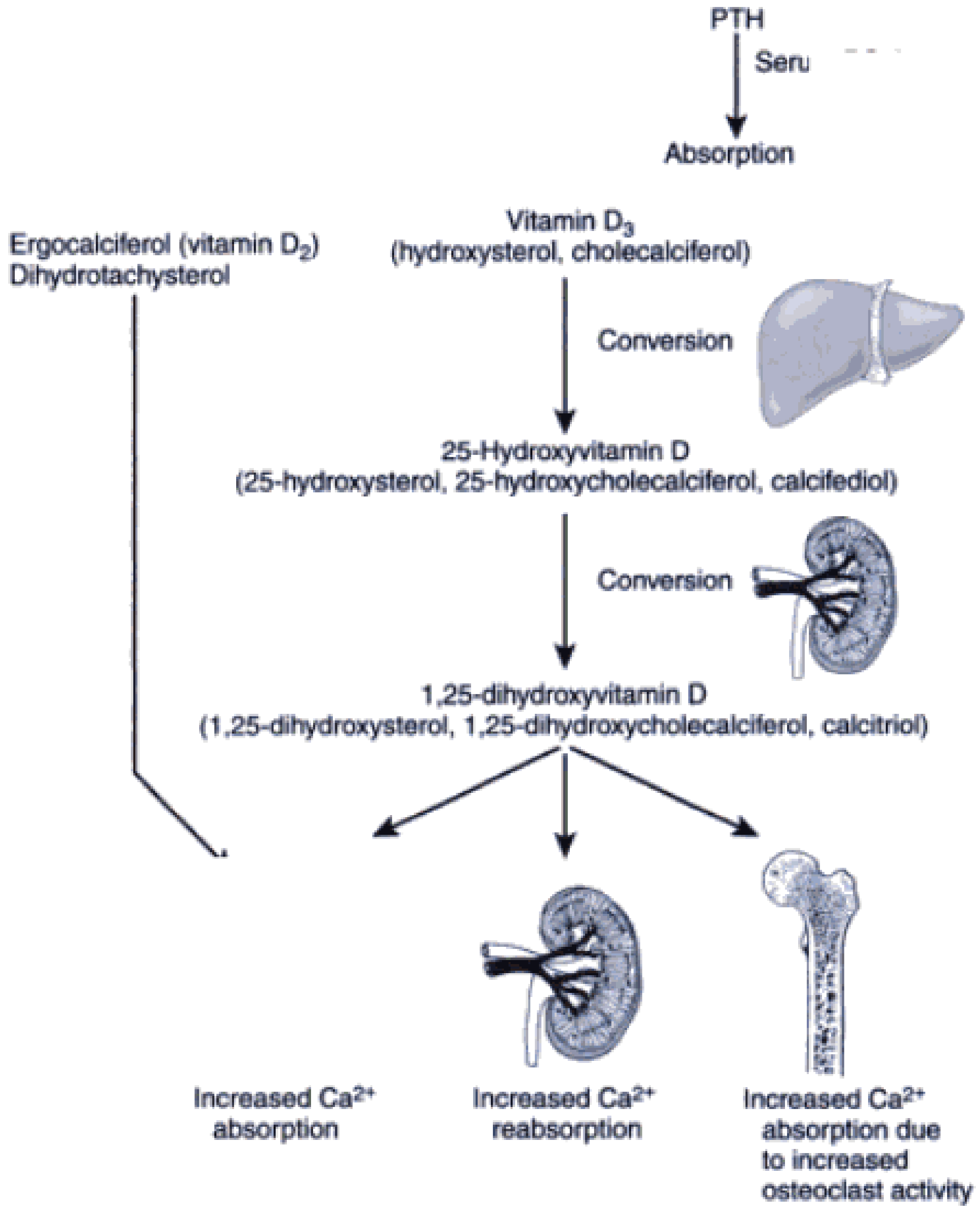
PTH
Seru
Absorption
Ergocalciferol (vitamin D_2)
Dihydrotachysterol
Vitamin D_3
(hydroxysterol, cholecalciferol)
Conversion
25-Hydroxyvitamin D
(25-hydroxysterol, 25-hydroxycholecalciferol, calcifediol)
Conversion
1,25-dihydroxyvitamin D
(1,25-dihydroxysterol, 1,25-dihydroxycholecalciferol, calcitriol)
Increased Ca^{2+} absorption
Increased Ca^{2+} reabsorption
Increased Ca^{2+} absorption due to increased osteoclast activity

Figure 32–4. Calcium is very closely regulated in the body through the combined effects of parathormone (PTH) and calcitonin. Vitamin D_3 serves as the mediator through its effects on the kidney, bone, and gastrointestinal tract. Vitamin D must undergo several sequential activations before it achieves its full effects as the dihydroxylated form. The active metabolite interacts with nuclear receptors, stimulating the formation of proteins that increase serum calcium levels. In addition to these indirect effects, PTH acts directly on the kidney and bone to increase serum calcium and decrease serum phosphorus. Calcitonin generally has the opposite effect.

tetany (muscle cramping, lameness, irritability), to muscle fasciculations and stiff gait, to tetanic seizures. The concentration of ionized calcium below which tetany develops has not been established. Indeed, cerebrospinal fluid concentrations may be more critical and may remain stable despite fluctuation in serum concentrations. Despite the importance of calcium in cardiac contractility, hypocalcemic dogs generally do not develop clinical evidence of cardiac dysfunction.

The need for calcium therapy can be based on serum calcium concentrations. Serum PTH concentrations also might prove useful in the diagnosis of hypoparathyroidism (Feldman and Nelson, 1996; Chew et al., 1996). Total serum calcium concentrations of 6.5 mg/dL might be considered critical; below 6 mg/dL generally results in clinical tetany, and below 4 mg/dL may be fatal. Although 50% of total serum calcium is bound to albumin and globulins, correcting serum calcium concentrations for serum protein deficiencies does not appear to improve the detection of hypocalcemia. On the other hand, patients with hypoproteinemia or hypoalbuminemia are not predisposed to hypocalcemia because ionized calcium concentrations remain normal. Hypocalcemic patients may be hyperphosphatemic as renal phosphorus excretion decreases. Hypomagnesemia (serum magnesium <1.2 mg/dL) may contribute to the development of hypoparathyroidism. Primary hypoparathyroidism in dogs can reflect destruction of the parathyroid glands by disease (lymphocytic parathyroiditis) or trauma, including surgical removal.

The most common cause of hypoparathyroidism in cats is injury or removal of the parathyroid gland after surgical removal of the thyroid glands. Secondary hypoparathyroidism can accompany several diseases in dogs, and treatment should be directed at both correction of hypocalcemia and the underlying cause if possible. Causes of secondary hypoparathyroidism include acute renal failure (e.g., ethylene glycol toxicity or urethral obstruction); chronic renal disease (increased PTH may not be able to adequately maintain serum calcium concentrations); acute pancreatitis; nutrition (diets containing low calcium to phosphorus ratios); and phosphate-containing enemas. Eclampsia or puerperal tetany is not an uncommon life-threatening cause of hypocalcemia in lactating bitches and queens.

Treatment of secondary hypoparathyroidism should include treatment of any underlying cause. Because PTH replacement is not possible (not commercially available), hypocalcemia and hyperphosphatemia initially should be treated with both calcium and vitamin D. Note that oral absorption of calcium may be insufficient until vitamin D replacement is adequate. Once vitamin D replacement is adequate and the patient is eating, oral calcium supplementation can be discontinued.

Hypocalcemic tetany is a life-threatening condition, requiring immediate IV replacement. Because calcium can

severe, the patient should be treated for hypercalcemia (see below).

Hyperparathyroidism (Hypercalcemia)

The most common cause of primary hyperparathyroidism is neoplasia (functioning adenoma) of the chief cells of the parathyroid gland (Feldman and Nelson, 1996). Hyperplasia of the parathyroid gland(s), multiple endocrine neoplasia, and hereditary hyperparathyroidism are less common causes. Secondary hyperparathyroidism generally occurs as calcium and phosphorus homeostasis becomes unbalanced (e.g., renal or nutritional secondary hyperparathyroidism). The commonality of causes of primary hyperparathyoidism is the loss of the normal feedback mechanism of calcium in the parathyroid gland. High circulating concentrations of PTH will increase calcium and phosphorus mobilization from bone. Initially, increased renal filtration and excretion of phosphorus maintain normal to slightly low serum phosphorus concentrations as the bone reabsorbs calcium in response to PTH. Hypercalcemia, hypophosphatemia, and hyperphosphaturia develop due to excess PTH and vitamin D. The sequelae of this classic triad include nephrogenic diabetes insipidus; initially increased, then decreased glomerular filtration rate; nephrocalcinosis; soft tissue mineralization; and fibrous osteodystrophy of all bones, but particularly the skull. Clinical signs include polyuria, polydipsia, listlessness, depression, inappetence, and weakness and muscle wasting. Muscle shivering or twitching may occur in some animals; vomiting and constipation, pancreatitis, renal failure, and gastrointestinal ulceration may also occur.

Hypercalcemia of malignancy results from tumor metastasis to bone, tumor-induced parathyroid hyperplasia, and production of bone-resorbing chemicals. A number of mediators are associated with the hypercalcemia of malignancy, including PTH-like peptides, vitamin D or related sterols, thyroid hormone, and prostaglandins. Hypervitaminosis D can result from excessive intake of vitamin D. Toxicity may not be evident until the drug has accumulated, which may take several weeks to months depending on the product. Occasionally, hypercalcemia may accompany hypoadrenocorticism or chronic renal disease. Hypercalcemia may also accompany bacterial or fungal osteomyelitis or other syndromes associated with inflammation and macrophages and lymphocytes that may secrete bone-resorbing factors. Hypercalcemia associated with rodenticide (cholecalciferol) toxicity can be lethal within 72 hours after ingestion.

Therapy of Hypercalcemia

Treatment of hypercalcemia should be aimed at correcting its underlying cause and preventing nephrocalcinosis. If calcium is sufficiently high to cause clinical signs (dehydration, uremia, cardiac arrhythmia, or neurologic dysfunction or weakness), symptomatic therapy should be implemented. Fluid therapy should correct fluid deficits and begin calciuresis. Physiologic saline at two to three times maintenance therapy is the fluid of choice because it promotes calciuresis. Potassium supplementation also may be necessary. Life-threatening hypercalcemia might be treated with an IV injection (25 to 75 mg/dog) of sodium ethylenediamine tetra-acetic acid (EDTA), which will chelate and thus reduce ionized calcium. EDTA is nephrotoxic, however, and acute renal failure may be a sequela of therapy.

Metabolic acidosis will increase ionized calcium as excess hydrogen ions displace calcium bound to serum proteins. Bicarbonate therapy may be indicated to correct the acidosis. Once fluid and acid-base deficits have been corrected in the hypocalcemic patient, potent diuretics (loop diuretics such as furosemide) will ensure maximal urinary sodium and thus calcium excretion. Glucocorticoids also promote calciuria and impair calcium absorption from the intestine and calcium resorption from bone. Glucocorticoids should be withheld, however, until the cause of hypercalcemia has been identified, particularly if lymphosarcoma is suspected, in order not to interfere with diagnosis and treatment. Phosphate also can be administered IV to lower calcium concentrations. Phosphonates (etridonate and pamidronate) are related to the metabolic byproduct pyrophosphate. They inhibit osteoclast activity. Poor oral bioavailability leads to IV administration. Veterinary doses have not been established for these drugs. Care should be taken with rate of administration. To avoid soft tissue mineralization, serum calcium and phosphorus concentrations should be monitored. Infusions should be stopped if serum phosphorus concentrations exceed 6.0 mg/dL or if calcium concentrations do not decrease or if they decrease by 2–3 mg/dL.

Calcitonin reduces osteoclast bone reabsorption and may cause a temporary decrease in serum calcium concentrations. The dose of (salmon) calcitonin has not been established for small animals; 400 to 1000 U have been administered in human patients, leading to a serum calcium concentration decrease of 3 mg/dL in about 4 to 12 hours. In veterinary medicine, the drug has been used to treat cholecalciferol rodenticide toxicity. Doses every 12 hours range from 4.5 to 8 U/kg SC in dogs and 4 U/kg IM in cats. Plicamycin is a cancer chemotherapeutic agent that can reduce serum calcium concentrations. Humans respond within 48 hours after a single dose; effects last for several days, but re-treatment may be required if the underlying cause of hypercalcemia is not treated. A dose of 0.5 μg/kg once or twice weekly corrected serum calcium concentrations in one dog (Feldman and Nelson, 1996).

Surgical correction of primary hyperparathyroidism may require postoperative management of hypocalcemia within 1 to 5 days after surgery, even in some patients with tumor excision (atrophy of normal tissue should be expected). Ultimately, both vitamin D and calcium can be withdrawn from animals whose parathyroid function becomes normal. Vitamin D therapy should be discontinued first by a gradual extention of the time between administrations; serum calcium concentrations should be checked at frequent intervals (see earlier discussion).

Secondary Hyperparathyroidism

Secondary hyperparathyroidism as a result of chronic renal disease reflects the abnormal calcium, phosphate, and calcitriol metabolism accompanying the syndrome. In human patients with renal failure, intestinal calcium absorption decreases (Hsu, 1997). Urinary calcium excretion also declines with progressive disease, probably due to decreased filter loads or increased parathyroid hormone. The balance between the two movements results in a slightly negative serum calcium balance, and balance can be maintained with appropriate dietary intake. In normal humans, the daily phosphate balance tends to be slightly negative or equally balanced. With declining renal function, phosphate concentrations increase. Phosphate restriction helps decrease the rate of progression of renal disease, which develops in part due to apparent calcium-phosphate deposition in the kidneys with subsequent interstitial fibrosis. In human patients, restricting phosphate intake can be sufficient to prevent secondary hyperparathyroidism either by increasing calcitriol and suppressing secondary hyperparathyroidism or by inhibiting parathyroid cell proliferation. Dietary restriction of phosphate is, however, difficult to achieve.

Although phosphate-binding agents help to control phosphate metabolism in renal failure, they also may be inadequate. Plasma calcitriol may be perceptibly decreased in early renal failure due to loss of renal tissue, phosphate retention, and inhibition of α_1-hydroxylase by uremic toxins (Hsu, 1997). This adaptation to renal disease is critical to prevent excessive calcium retention and tissue calcification. Thus, use of calcitriol and oral calcium supplementation to maintain calcium balance in patients with renal disease is implemented most safely in those patients in whom a negative calcium balance can be maintained. Restriction of phosphate intake alone currently remains the most appropriate mechanism for maintaining calcium-phosphate balance in the patient with renal disease. Future therapies may include ferric ammonium citrate: ferric salts apparently precipitate phosphate in the intestinal lumen, limiting its absorption (Hsu, 1997).

DISEASE OF THE PANCREAS: DIABETES MELLITUS

Normal Physiology

Glucagon stimulates liver conversion of glycogen into glucose and the metabolism of noncarbohydrates, such as amino acids and lipids, into glucose or glucose precursors (lipids to fatty acids and glycerol). Low blood glucose concentrations stimulate glucagon release from α-cells of the pancreas. Should glucose concentrations become too high, insulin secretion is stimulated from the β-cells of the pancreas. Insulin's effects are the exact opposite of those of glucagon: It acts to decrease blood glucose. Insulin stimulates the formation of glycogen from glucose in the liver and inhibits the peripheral formation of glucose from amino acids and lipids. The peripheral effects of insulin on insulin-dependent tissues such as muscle and adipose tissue are to facilitate diffusion of glucose through cells. As a result, amino acids are synthesized in muscle, and fat is synthesized and stored in adipose cells. Insulin is also regulated by a negative feedback that is sensitive to glucose concentrations in the blood. As glucose concentrations decrease, less insulin is released from the pancreas, and blood glucose no longer declines. As insulin concentrations decrease, insulin-dependent cells can no longer utilize blood glucose, whereas insulin-independent cells, such as neurons (which obtain glucose by simple diffusion), can continue to use any glucose that remains in the blood.

Diabetes is a progressive disease characterized by four stages in human patients. Prediabetic patients are normal but subsequently develop the disease; subclinical diabetes can only be diagnosed by sophisticated provocative tests; latent diabetics are clinically normal but respond abnormally to glucose; and overt diabetics have persistently high fasting blood glucose concentrations. The duration of progression from stage I to stage IV can be weeks to years, depending on the type of diabetes.

Diabetes mellitus has been classified in small animals as type 1 and type 2. Type 1 is insulin dependent (IDDM), whereas type 2 diabetes is non-insulin dependent (NIDDM) and develops despite adequate secretion of insulin (Nelson, 1992). Causes of type 1 diabetes in animals may include hereditary factors and pancreatic destruction by pancreatitis, viruses, or autoimmune disease. Type 2 diabetes may reflect a relative insulin deficiency. A set point that controls blood glucose may be reset at a point that is too high; insulin secretion by pancreatic islet cells may not be sufficient to match the hyperglycemic state. Although glucose uptake by peripheral tissues is impaired, and glucose synthesis continues by the liver, the ketotic state is generally avoided by the presence of some insulin. The sequelae of β-cell insensitivity to glucose can be worsened if peripheral receptors become less sensitive to insulin, as might occur in obesity; in the presence of diabetogenic hormones such as glucocorticoids, T_4, glucagon, growth hormone, progesterone, or epinephrine; or in the presence of selected drugs including glucocorticoids and progestogens.

A third class of diabetes has been used to describe the preclinical or sublatent diabetic dog or cat. In contrast to human diabetics, animals with type 2 diabetes may progress to type 1 diabetes. Diabetic patients (especially cats) can appear clinically normal despite therapy for months to several years before the disease progresses. Cats may move between both classes. Non–insulin-dependent diabetes in the cat may remain sufficiently compensated for long periods of time with clinical signs of diabetes and insulin dependence more likely to develop during periods of stress or with obesity.

The importance of dietary management of NIDDM patients needs to be underscored because these patients may not respond to insulin therapy. Therapy is complicated in animals that are insulin dependent by the return of the non–insulin-dependent state.

Overt diabetes is diagnosed by persistent hyperglycemia (>200 mg/dl). However, a definitive diagnosis of diabetes mellitus may be difficult to make. Mild hyperglycemia such as that induced by stress or selected diseases (e.g., hyperadrenocorticism) may result in glucosuria. In cats, blood glucose concentrations may reach 400 gm/dL in the nondiabetic state. Thus, diagnosis of diabetes must be based on blood glucose and the presence of the classic signs of diabetes: polydypsia, polyuria, polyphagia, and weight loss. Unfortunately, these clinical signs are not unique to diabetes and other differentials must be considered. Hospitalization of the patient and reevaluation of blood glucose after the patient has adjusted to the new

ber of body tissues influenced by endogenous glucocorticoids. The reader is referred to the chapter on glucocorticoid therapy (Fig. 32–5). No screening test stands out as the best; each has strengths and weaknesses. Diagnosis is best based on history, physical examination, and ACTH stimulation or low-dose dexamethasone suppression.

Baseline and Provocative Testing

Cortisol is the major glucocorticoid secreted by the adrenal gland. Baseline cortisol concentrations can be studied with a variety of tests that detect both cortisol and corticosterone. Diagnosis of hyperadrenocorticism can be supported by several screening tests (Feldman, 1983, 1996; Guptill, 1997; Peterson, 1994, 1982). The urinary cortisol-to-creatine ratio is a simple, effective screen for spontaneous hyperadrenocorticism in the patient with normal renal function. Resting (morning) cortisol concentrations are not beneficial by themselves, but they can be used in conjunction with provocative tests. The ACTH stimulation test is the most common screening test. Animals with maximally responding adrenal glands should respond to ACTH stimulation by secreting large amounts of cortisol. Low- and high-dose dexamethasone suppression tests provide further confirmation of iatrogenic versus spontaneous hyperadrenocorticism as well as discrimination among causes of spontaneous disease (Feldman, 1983, 1996).

Several protocols have been described for the ACTH test. The animal should be fasted for 12 hours; testing begins before 10 AM. After collection of a baseline sample, 0.125 mg (cats) and 0.25 mg/kg (dogs) of synthetic ACTH is given intramuscularly (or IV in the cat) or 2.2 IU/kg porcine ACTH gel is given intramuscularly (dog and cat). Plasma cortisol is collected at 30 and 60 minutes in cats and 60 minutes in dogs for the synthetic ACTH. For porcine ACTH, samples should be collected 2 hours after injection for the dog and at 1 and 2 hours for the cat. Normal values should be determined by each laboratory. Most laboratories, however, use similar assays.

In general, normal baseline cortisol concentrations are between 0.5 and 6.0 μg/dL in dogs. In dogs at 60 minutes, cortisol concentrations between 17 and 20 μg/dL are borderline, and concentrations more than 20 μg/dL are suggestive of hyperadrenocorticism. In cats at 30 minutes, cortisol concentrations less than 13 μg/dL after ACTH are normal; between 13 and 15, borderline; and more than 15.0 μg/dL, suggestive of hyperadrenocorticism. Ratios of baseline to poststimulation cortisol concentrations do not appear to be informative. Up to 20% of dogs with spontaneous hyperadrenocorticism will respond normally to ACTH; thus the

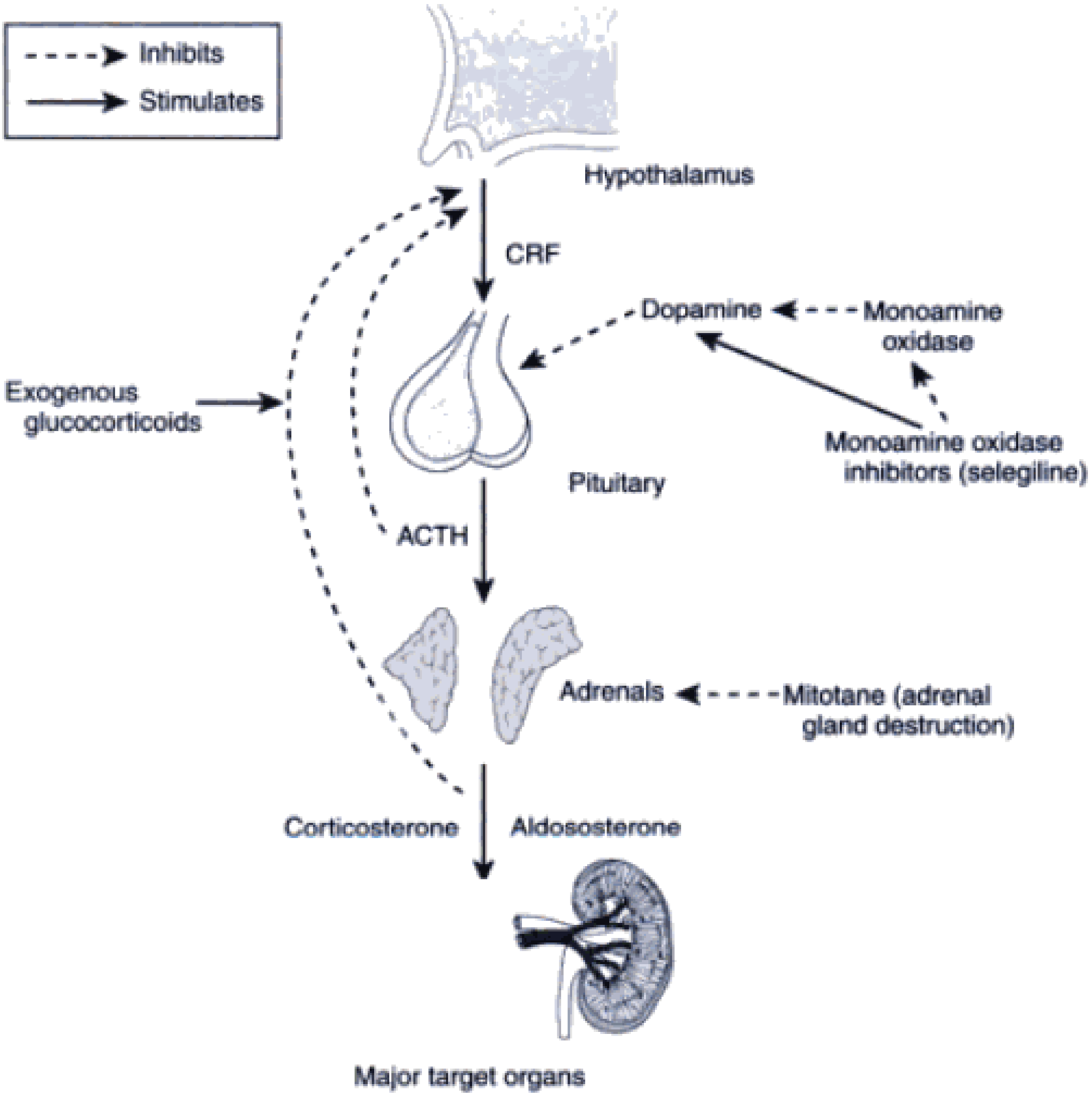

Figure 32–5. The relationship between the hypothalamus, pituitary, and adrenal glands. Dopamine appears to be important to the negative control of adrenocorticotropic hormone (ACTH) release from the pituitary gland in dogs. Re-establishment of adequate dopamine concentrations through the use of monoamine oxidase inhibitors (which prevent the breakdown of dopamine) tends to normalize the axis in dogs with pituitary-dependent hyperadrenocorticism, thus perhaps prolonging the time that can elapse before less desirable drugs must be used (e.g., mitotane). Mitotane controls hyperadrenocorticism by virtue of its nonselective destruction of the adrenal gland. CRF = corticotropin-releasing factor.

test is not absolutely reliable and should be used in conjunction with clinical signs as a screening test (Feldman and Nelson, 1996).

Chronic nonendocrine diseases, including unregulated diabetes, can complicate interpretation due to both false-negative and false-positive results. Because adrenal tumors often retain surface ACTH receptors, approximately 60% of dogs with hyperadrenocorticism associated with adrenal tumors will respond in an exaggerated fashion to exogenous ACTH (Feldman and Nelson, 1996), whereas up to 40% may have a normal test. The ACTH stimulation test is the best method for discriminating between spontaneous and iatrogenic hyperadrenocorticism. A low normal baseline cortisol with little to no response to exogenous ACTH suggests iatrogenic hyperadrenocorticism. The ACTH test also should be used to monitor patients receiving Lysodren (or selegiline) therapy.

In the normal animal, a low dose of dexamethasone will suppress ACTH secretion, and plasma cortisol concentrations should rapidly decrease (within 1 to 3 hours), remaining suppressed for 24 to 48 hours. Cortisol should decrease to less than 1 μg/dL in the normal dog and cat for 8 hours after treatment with 0.01 mg/kg dexamethasone IV. Concentrations between 1.0 and 1.4 μg/dL are nondiagnostic (Feldman and Nelson, 1996). Dexamethosone should be used because it will not cross react with test reagents. Patients with pituitary-dependent tumors, hyperadrenocorticism, or adrenocortical tumors will continue to secrete cortisol, and suppression will not occur. A retrospective study of dogs with hyperadrenocorticism submitted to necropsy found very good correlation between the low-dose dexamethasone and ACTH response test (agreement in 11 of 12 patients) (Van Lieu et al., 1997).

Endogenous ACTH concentrations (range of 10 to 110 pg/mL; average 45), if available, can be used to distinguish pituitary-dependent hyperadrenocorticism from adrenal tumors. The laboratory of submission should be contacted before collection to identify the correct sampling vial (e.g., chilled, nonglass vials containing EDTA) and sample handling (e.g., immediate harvesting of plasma and freezing). Addition of aprotinin may facilitate accuracy of ACTH (Feldman and Nelson, 1996). Samples should be collected between 8 and 9 AM after an overnight hospitalization. Less than 10 pg/mL is suggestive of an adrenocortical tumor; concentrations of 45 pg/mL or greater are consistent with (not diagnostic of) pituitary-dependent hyperadrenocorticism. The high-dose dexamethasone suppression test might also distinguish between pituitary-dependent disease and adrenal tumors. High doses of dexamethasone are generally sufficient to cause the overactive pituitary gland to decrease ACTH secretion. The adrenal tumor will not, however, be inhibited. After collection of a baseline cortisol concentration, 0.1 mg/kg dexamethasone is given IV, and a second sample is collected 4 to 8 hours later. Suppression is defined as a 4- to 8-hour plasma cortisol level less than 50% of the baseline. Approximately 25% of dogs with pituitary-dependent hyperadrenocorticism will not suppress. The low-dose and high-dose dexamethasone tests are usually performed in tandem.

Therapy

The goal of drug therapy for hyperadrenocorticism is to normalize cortisol secretion by the hyperplastic adrenal glands (Feldman et al., 1992b; Kintzer and Peterson, 1994; Feldman and Nelson, 1996). Currently, there is no drug therapy that will cure the pituitary-dependent hyperadrenal patient. Life-long therapy should be anticipated. Mitotane, or o,p′-DDD (Lysodren) has been the drug generally recognized for treatment of pituitary-dependent hyperadrenocorticism and is useful only in dogs (Feldman et al., 1992b; Feldman and Nelson, 1996; Peterson and Kintzer, 1997). A chlorinated hydrocarbon, mitotane is adrenocorticolytic, causing progressive necrosis of the zona fasciculata, zona reticularis, and zona glomerulosa. The toxin is specific for the adrenal glands, particularly the hyperplastic gland, with one exception. In normal animals, mitotane has caused fatty degeneration and centrolobular atrophy of the liver. Although the disposition of mitotane has not been well established in dogs, safety has been studied in a small number of animals. Normal animals tolerate the drug at 50 mg/kg 5 days out of 7 for months with no apparent adverse effects. Adrenocortical function will, however, be impaired.

Therapy of hyperadrenocorticism with mitotane occurs in two phases: an induction phase and a maintenance phase (Feldman and Nelson, 1996; Peterson and Kintzer, 1997). For induction, o,p′-DDD is dosed 25 mg/kg every 12 hours until clinical signs of hyperadrenocorticism begin to resolve. Specifically, water consumption should decrease to less than 60 mL/kg per day. The animal's appetite should return to normal; the rate of ingestion of the meal may be the earliest indicator of effective therapy. The animal should be fed two meals per day, one before each treatment. Therapy should be discontinued if the patient vomits or diarrhea develops. The time to response will vary with each animal. Most will respond in 7 to 14 days, with an average time to response of about 11 days in dogs. If a therapeutic end point has not been reached by 21 days of therapy, an alternative diagnosis should be considered. Some dogs may, however, take 60 days or longer to respond. The ACTH response test should be performed weekly during induction to monitor response to therapy and to document the end point of induction. Maintenance therapy is indicated when baseline and post-ACTH cortisol concentrations are less than 5 μg/mL.

Maintenance therapy will be necessary for the rest of the animal's life, although the dose and frequency may vary. In the absence of maintenance therapy, the adrenal glands will once again become hyperplastic in response to continued ACTH secretion from the pituitary gland. The more rapid the response of the animal to induction therapy, the more sensitive the animal is to mitotane, and the lower the maintenance dose will need to be. Rapid responders (within 10 days; sensitive animals) begin treatment at 25 mg/kg and resistant dogs at 50 mg/kg once a week. The ACTH response test is repeated at 1- to 3-month intervals and used as a basis for interval or dose adjustment. Concentrations in either the baseline or the response test indicate that the dose needs to be increased or the interval shortened. Relapses should be expected and reacted to accordingly.

If clinical signs of hyperadrenocorticism are not evident before therapy is begun, evidence of mitotane toxicity must be more closely sought in order to guide dose adjustment. Adverse reactions to an overdose generally manifest as anorexia, vomiting or diarrhea. Overdosing is not unusual because dogs generally require life-long therapy. If adverse reactions develop with the recommended dose, they generally appear on the third or fourth day of therapy; therapy might begin on a weekend to ensure easier contact between the pet owner and the veterinarian. The drug can be discontinued for a brief period (3 to 4 days) if gastric irritation, weakness, or other signs of toxicity develop. Dose reduction may be necessary for some animals that develop adverse reactions. Adverse reactions also can be treated by supplementation with glucocorticoids (5 to 10 mg prednisolone) as long as clinical signs persist; mitotane should be discontinued during this time.

Routine administration of glucocorticoids during mitotane therapy is discouraged because it will be difficult to monitor clinical signs or the ACTH stimulation test if the patient is continuing to receive glucocorticoids (Spencer et al., 1980; Toutain et al., 1994). The patient must have been off glucocorticoid therapy for at least 3 days before an ACTH response test is performed. Very rarely, mitotane therapy can cause a deficiency of mineralocorticoid and subsequent electrolyte abnormalities. Prednisolone has some mineralocorticoid activity (triamcinolone has little and dexamethasone none) and may be sufficient for mineralocorticoid supplementation in such cases. Alternatively, a mineralocorticoid such as fludrocortisone may be indicated.

Occasionally, some animals develop central nervous system signs of mitotane toxicity, including apparent blindness, ataxia, head pressing, and aimless wandering. These signs may not appear for several months to years after therapy is begun, and other diagnoses (i.e., central nervous system tumors) must be ruled out. The drug should be discontinued for 3 to 4 days; dose reduction may be necessary for some animals that develop adverse reactions.

If therapy for hyperadrenocorticism is successful, other clinical signs of the disease or its complications will gradually resolve. Urinary tract infections should resolve in several weeks (antibiotic therapy may be necessary); an estrous cycle in anestrous patients may occur within several months of completing therapy. Resolution of some clinical signs (e.g., skin manifestations, calcinosis cutis, nonhealing wounds) will take 3 to 6 months or longer. Development of a puppy coat or a change in hair color may occur. Resolution of clinical laboratory changes (i.e., liver enzymes and cholesterol) may take up to 18 months. The diabetic cushingoid animal will require more careful monitoring because insulin resistance will decrease as mitotane therapy becomes effective. Generally, large doses of insulin are necessary to control clinical signs of diabetes in these animals (see earlier discussion) until the adrenal gland is no longer hyperactive. Urine should be checked for glucose several times during the day as mitotane therapy is begun; a negative result indicates that the insulin dose needs to be reduced by about 20%. Some diabetic animals may not require insulin therapy after their adrenal disease is successfully treated.

Lack of response to mitotane therapy indicates a diagnosis other than hyperadrenocorticism, or non–pituitary-dependent hyperadrenocorticism. Other causes of hyperadrenocorticism include an adrenocortical tumor or iatrogenic hyperadrenocorticism. Other diseases that cause polyphagia, polydipsia, and polyuria must be ruled out. Included in this category are diabetes mellitus and the effects of drugs such as anticonvulsants. Occasionally, therapeutic failure results from an old drug that has lost its potency. The dose may be too low; some animals may require doses up to 150 mg/kg per day for 1 to 2 months.

Selegiline (L-deprenyl) is a monoamine oxidase inhibitor. These compounds inhibit the degradation of biogenic amines and, most notably, dopamine. Thus, they are used to treat dopamine-deficient conditions such as Parkinson's disease in human patients. Many of the human diseases responsive to selegiline are age related. This includes pituitary-dependent hyperadrenocorticism. Restoring dopamine may inhibit oversecretion of ACTH (see Fig. 32–5). Unlike other monoamine oxidase inhibitors, selegiline is specific for monoamines in the brain (monoamine oxidase B); hence it is a safe drug. The net effect is "normalization" of dopamine concentrations in the brain. Regulation of the hypothalamic-pituitary axis is improved, resulting in correction of the hyperactive adrenal gland without causing hypoadrenocorticism. The drug has been studied for treatment of pituitary-dependent hyperadrenocorticism in dogs at 1 to 2 mg/kg per day and was successful in five of seven dogs. Side effects are rare, even at several times the dose.

As with other drugs, therapy must be for the lifetime of the animal (Bruyette et al., 1997). Treatment should begin at 1 mg/kg orally once a day for 30 days. If no response has occurred by that time, the dose should be doubled for an additional 30 days. Failure to respond at that time may indicate the need for an alternative therapy. The primary disadvantage of selegiline is its cost. Several generic versions of L-deprenyl are available. Although the bioequivalency of the generic preparations is the same among themselves, however, they all differ (are less bioavailable) from the original product, L-deprenyl (Eldepryl). Comparisons with the animal product Anipryl are not available. Thus, it is wise to avoid the generic oral preparations until studies have established the appropriate dose for dogs. Deprenyl might be used to delay the time before mitotane must be started. However, the use of deprenyl was recently studied in 10 dogs with PDH (Reusch, 1999). The dogs were studied for 6 months at a dose of 2 mg/kg once daily. The study found no differences in serum cortisol at the beginning or end of the study; the disease of only 4 of the 10 dogs was successfully suppressed by the study's end. These findings suggest that deprenyl may not be useful as the sole agent for treatment of PDH. The combined use of mitotane and deprenyl warrants consideration, with mitotane providing a rapid response but deprenyl providing maintenance control.

Several other drugs have been used with variable degrees of success in hyperadrenal animals that cannot tolerate mitotane. Antiserotonin drugs such as cyproheptadine (0.3 to 3 mg/kg once daily orally) act to prevent serotonin-mediated release of ACTH from the pituitary. These drugs are characterized by a low success rate; in addition, serotonin suppresses the appetite, and antagonism by cyproheptadine increases the appetite. Bromocriptine (0.05 mg/kg every 12 hours orally) is a dopamine agonist that has been used to treat some human patients with pituitary-dependent diseases, particularly those that are associated with prolactin-secreting and growth-hormone-secreting pituitary tumors. Efficacy in dogs with pituitary-dependent hyperadrenocorticism (doses ranging from 0.01 to 0.1 mg/kg) has

(growth hormone–releasing hormone) and inhibiting (somatostatin) factors released from the hypothalamus in response to complex neurohumoral regulatory mechanisms. Neurogenic stimuli include adrenergic (α), dopaminergic, and cholinergic stimuli; metabolic factors that cause GH secretion include nutrient metabolites and hypoglycemia. Secretion of GH results in feedback inhibition to and subsequent release of somatostatin from the pituitary gland.

Diseases involving GH usually result from GH deficiency or GH excess. Conditions associated with a deficiency include pituitary dwarfism and GH-responsive dermatosis. Acromegaly is a disease associated with excessive secretion of GH in response to progesterone therapy or spontaneous disease. Clinical signs of growth hormone deficiency include abnormal growth. Dermatologic manifestations include bilaterally symmetric alopecia of the trunk and severe hyperpigmentation. Clinical signs of acromegaly reflect either anabolic or catabolic abnormalities. The most common is inspiratory stridor (due to soft tissue accumulation in the thorax) and its accompanying sequelae. Increased body size results from proliferation of bone and connective tissues, particularly of the limbs, feet, head, and abdomen. Thickening of the skin may be present. Catabolic effects result in insulin antagonism and manifest as signs typical of diabetes.

Diagnostics: Provocative Testing

Deficiency

Changes in GH concentrations in response to stimulation can be used to diagnose disorders of GH secretion. Clonidine and xylazine are α-adrenergic agonists that will cause increases in circulating GH. The dose for clonidine varies (3 to 30 μg/kg); higher doses have been associated with longer periods of hyperglycemia, aggression, and sedation compared with xylazine (100 to 300 μg/kg). Plasma samples for both tests should be collected before administration and at 15, 30, 45, 60, and 90 minutes after administration. Dogs with GH deficiencies do not respond to clonidine or xylazine. Xylazine is a sedative used as a small animal anesthetic agent that is structurally similar to clonidine. Growth hormone–releasing factor has been studied in dogs. Administration of human GH-releasing hormone increased serum GH twofold to fourfold in normal dogs compared with no increase in dogs with suspected GH deficiency.

Hypersecretion

Provocative testing for the diagnosis of acromegaly has not been reported in dogs; basal GH concentrations can be used diagnostically. Growth hormone is stable at −20°C for prolonged periods of time.

Therapy

Deficiency

Growth hormone is available as human, beef (10 IU subcutaneously every other day for 30 days), and pork (2 IU subcutaneously every other day for 100 days). Beef and pork at 0.3 IU/kg subcutaneously (divided into two or three doses each week) are biologically active in the dog. Therapy should be discontinued once dermatologic signs have resolved.

Hypersecretion

Progesterone therapy should be discontinued if it causes acromegaly. If β-cell activity of the pancreas has become impaired, permanent diabetes mellitus may develop. Currently, no medical management has proved effective for treatment of acromegaly in animals.

Diabetes Insipidus

Diabetes insipidus results from either a deficiency in vasopressin secretion or its interaction with its target receptors in the distal and collecting tubules of the kidney. Vasopressin is secreted, along with oxytocin, from the neurohypophysis. It differs from oxytocin by only two amino acid substitutions. Changes in plasma osmolality and blood volume are the major stimuli that cause release of vasopressin.

Vasopressin is associated with both pressor and antidiuretic effects; the primary effect can be manipulated by structural changes. Whereas arginine vasopressin (AVP) is the predominant hormone in most animals, it is associated with strong pressor actions. Substitution of D-arginine for L-arginine (at amino acid 8) and modification of cysteine yields a powerful antidiuretic. The resulting chemical is 1-deamino-(8-D-arginine) vasopressin (DDAVP, desmopressin), which is the commercially available synthetic product. Arginine vasopressin interacts with receptors in vascular smooth muscle (V_1 phosphatidylinositol-dependent receptors) and renal epithelial cells (V_2, c-AMP-dependent receptors). The analogue DDAVP primarily interacts with V_2 receptors.

In the collecting duct, vasopressin "opens pores" in the cell membranes of the duct epithelium, allowing water and solutes to follow a concentration gradient. Hence, fluid moves into the hyperosmotic environment surrounding the ducts. The vascular system (vasa recta) surrounding the ducts distributes the water into systemic circulation. The hyperosmotic environment surrounding the collecting ducts is maintained, and urine production decreases. Up to 90% of the fluid filtered by the glomerulus and not absorbed in the proximal nephron will be reabsorbed under the presence of vasopressin. In the absence of vasopressin, the permeability of the distal and collecting tubules becomes resistant to movement of water or solutes (most notably urea). The hypotonic filtrate formed in the proximal nephron is eliminated unchanged, resulting in a water diuresis characterized by a large volume of urine with a low osmolality.

Vasopressin deficiency, or central diabetes insipidus, results from insufficient AVP (total or partial) release from the pituitary. Polyuria and polydipsia are the clinical signs that tend to catch the attention of pet owners. Animals with partial insufficiency can concentrate urine but rarely above 1.015 to 1.020. Nephrogenic diabetes insipidus reflects an inability of the distal and collecting ducts to respond to AVP. The modified water deprivation test is used to distinguish the causes of polyuria and polydipsia. Plasma vasopressin concentrations also may help distinguish between central and nephrogenic diabetes insipidus. Finally, provoc-

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33 Dermatologic Therapy

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INTRODUCTION
ANATOMY AND PHYSIOLOGY OF THE SKIN AS IT RELATES TO DRUG THERAPY
PRINCIPLES OF TOPICAL DRUG THERAPY
Drug Movement and the Skin
Vehicles
  Characteristics of a Vehicle
  Types of Vehicle
Classes of Topical Drug
  Antiseborrheics
  Retinoids
  Ceruminolytics
  Antipruritics
  Irritants
  Antimicrobials
  Antiparasitics
SYSTEMIC DERMATOLOGIC THERAPY
Antimicrobials
Anti-inflammatory/Antipruritic Agents
  Glucocorticoids
  Dapsone
  Antihistamines
  Omega-3 (Omega-6) Polyunsaturated Fatty Acids
  Behavior Modifiers
Antiparasitic Drugs
  Cythioate
  Macrolide Antibiotics
Immunomodulators
TRANSDERMAL DELIVERY OF DRUGS
TREATMENT OF SPECIFIC DERMATOLOGIC DISORDERS
Chronic Pruritus
  Pathophysiology
  Drug Therapy
Acral Lick Dermatitis
Canine Seborrhea
Generalized Demodicosis
Dermatophytosis

INTRODUCTION

A major advantage of treating diseases of the skin is easy access to the site of disease. Drug delivery can be facilitated by topical therapy, and response can be based on visual examination (clinical signs) rather than solely on supportive diagnostic aids. The advent of topical drug therapy has also, however, led to a plethora of systems designed to deliver drug to the skin, its upper layers, through the skin, and, in some instances, into systemic circulation. The result is an innumerable list of products that vary in active and inactive ingredients. This chapter approaches treatment of skin diseases by first discussing drugs that are intended for topical administration and then drugs intended for systemic therapy. Finally, specific skin diseases are addressed.

ANATOMY AND PHYSIOLOGY OF THE SKIN AS THEY RELATE TO DRUG THERAPY

The skin is the largest organ of the body, accounting for 12% of body weight in the adult dog and 24% in the puppy (Pavletic, 1991). Although structurally canine and feline skin markedly varies from human skin, some similarity is maintained among the species. Generally, skin is thickest on the head, dorsum, and plantar and palmar surfaces of the feet; thinner on the ventral abdomen, medial aspects of the limbs, and inner pinnae; and thinnest on the scrotum (Riviere and Spoo, 1995). The skin is perforated by several appendages, the number and structure of which varies among the species. In cats and dogs, these include hair follicles, sebaceous and sweat glands, and nails.

Histologically, the skin is composed of the epidermis and dermis. Dermis is essentially composed of connective tissue, including collagen, elastin, and reticular fibers, and amorphous ground substance. It can be roughly separated into a dense, deeper reticular layer that connects the dermis to the hypodermis (composed mostly of fat) and a more superficial, loosely packed papillary layer. The dermis contains an arterial and venous network that provides nutrients to the epidermis and receives topically administered drugs able to penetrate this region, which distribute to the rest of the body (Riviere and Spoo, 1995). Cutaneous blood flow rates can affect percutaneous absorption of drugs. Cutaneous blood flow in the dog and cat is greatest in the skin of the ventral abdomen and pinnea (Riviere and Spoo, 1995). This fact, coupled with skin thickness, leads to these regions serving as the site of drug delivery for many topically applied drugs intended to have systemic effects.

The epidermis is composed of stratified squamous keratinized epithelium that undergoes sequential superficial differentiation. Five layers of keratinocytes exist, with the stratum basale being deepest followed by the stratum spinosum, stratum granulosum, stratum lucidum, and, the most superficial layer, stratum corneum. Among these layers, the stratum corneum is the most important to topical drug therapy because it is the primary barrier. The stratum corneum consists of several layers of dead cells, which present a significant lipid barrier to drug penetration. The thickness varies with the area of the body. The cells are aligned to minimize water loss and are surrounded by a plasma membrane that serves as a barrier to movement into or out of the skin (Riviere and Spoo, 1995).

The epidermis is anaerobic (Riviere and Spoo, 1995) because of the absence of capillaries that directly provide oxygen to the cells (Riviere and Spoo, 1995). Despite the fact that 80% of the total energy requirements of the skin occur by anaerobic glycolysis, the skin is metabolically active. Drugs that are able to pass through the corneum potentially are subjected to drug-metabolizing enzymes similar to those in the liver. The skin has a great capacity to synthesize lipids, which are located in the extracellular (intercellular) material, the primary barrier to drug penetration in this region of the epidermis (Riviere and Spoo, 1995). Lipids are important to intercellular cohesion, permeability (barrier), function, and normal desquamation of mature corneocytes (White, 1995). Epidermal lipids include both free and esterified fatty acids, sphinglolipids, free and esterified cholesterol, and phospholipids (White, 1995). The lipids form a bilipid layer, with the hydrophobic and hydrophilic ends aligning within themselves (Riviere and Spoo, 1995). As the epidermis differentiates, the fatty acid component tends to increase. Alterations in the lipid layer result in the release of arachidonic acid and the subsequent formation of inflammatory mediators. Keratin is the major protein of the skin and is the foundation of the hair (Riviere and Spoo, 1995).

PRINCIPLES OF TOPICAL DRUG THERAPY

Topical drug therapy is indicated as initial therapy until a definitive diagnosis can be made (i.e., while waiting for results from diagnostic tests), as an adjunct to systemic therapy, and as sole treatment for selected specific dermatologic diseases. A definitive diagnosis of the cause of the skin disease should be made if possible before any masking treatments have been initiated. Therapy may be based on the morphology of skin lesions if further diagnostics yield no useful data. The clinician must be able to distinguish between primary and secondary lesions. Primary lesions develop as a direct result of the underlying disease. Secondary lesions may evolve from the primary lesion, trauma (e.g., scratching) induced by patient response to the lesion, or medications. The clinician must also be able to recognize or discriminate between acute versus chronic, deep versus superficial, or benign versus malignant lesions.

Clinicians should be very familiar with one or two drugs from each class (e.g., one keratolytic, two topical antifungals). Lesions should be evaluated frequently to assess therapy and the need to modify treatment because of treatment failure or adverse effects. The clinician must know the adverse effects of each drug and anticipate and look for evidence of these effects. Clients must be well educated regarding topical drug agents and the need for compliance. Several principles can guide effective use of dermatologic agents.

Drug Movement and the Skin

The skin functions as a barrier to prevent loss of water, electrolytes, and macromolecules and to exclude external agents (chemical, physical, and microbiologic) from the internal environment. The stratum corneum is the layer of the epidermis that is primarily responsible for this physical barrier because of the abundance of keratin and the configuration and content of the intercellular lipids. Topically applied drugs can be absorbed by three routes; they are, in order of importance or magnitude, the stratum corneum (between rather than through the cells), hair follicles, and sweat or sebaceous glands. Movement of drug through the stratum corneum occurs by passive diffusion. Only a very small proportion of topically applied drug penetrates the stratum corneum. Despite the alignment of the lipid layer, both lipid-soluble and water-soluble drugs can pass through the stratum corneum, although passage may occur through the appendages. More drug is likely to pass through the skin of heavily haired animals because of the larger number of hair follicles.

Before a drug can move through the stratum corneum, it must first move out of the vehicle. Thus, factors that affect percutaneous absorption are not limited to the drug but include factors involving the vehicle. Drug movement through the skin has been mathematically described (Fick's law) (Riviere and Spoo, 1995) to be directly proportional to the partition coefficient between the vehicle and the stratum corneum, the concentration of drug dissolved in the vehicle, the diffusion coefficient, and the surface area of the skin to which the drug is applied. Percutaneous absorption is inversely proportional to the depth of the stratum corneum (and additional layers). The driving force for absorption, as with any drug movement, is concentration of diffusible drug. The higher the concentration of dissolved drug in the barrier (stratum corneum), the greater the diffusion "gradient." Drugs with a high degree of lipid solubility achieve higher concentrations in the stratum corneum because it is lipophilic. Large drug molecules are absorbed less readily.

Vehicles

A vehicle is a substance used in a medicinal preparation as the agent for carrying the active ingredient. Occasionally, the vehicle is therapeutic, but usually it is inactive. The vehicle of a topical agent can profoundly affect movement of drug into the skin. Two topical medications may have the same active ingredient at the same concentration but have different vehicles and thus markedly differ in efficacy. A drug must be sufficiently soluble in a vehicle such that it can distribute throughout the vehicle and thus come in contact with the skin in diffusible form. It cannot, however, be so soluble in the vehicle that it does not leave the vehicle and thus penetrate the skin. Vehicle selection is critical to effective topical therapy. A vehicle not only acts as a carrier but also can have a direct impact on the skin and thus on drug movement.

Characteristics of a Vehicle

The physical and chemical characteristics of the vehicle and the drug largely determine drug movement. The partition coefficient describes the relative affinity of a hydrophobic phase and a hydrophilic phase. The greater the partition coefficient, the greater the affinity between the drug and the lipid phase of the skin, which generally results in an increase in percutaneous absorption of the drug. Once the skin is penetrated, however, the drug must be able to leave the lipid phase of the skin if it is to reach systemic circulation. Drugs with very high partition coefficients tend to remain in the lipid layer, causing a reservoir effect. A partition coefficient of 1 is desired for topical medicaments (Riviere and Spoo, 1995).

The rate of vehicle penetration through the stratum corneum also influences percutaneous absorption. If vehicle penetration of the stratum corneum is more rapid than penetration of the skin, the concentration of drug in the vehicle on the surface of the skin increases, perhaps to the point of precipitation, slowing absorption. Evaporation of the vehicle will cause the same effect (Riviere and Spoo, 1995). Some vehicles are used to facilitate drug movement into the skin. For example, dimethylsulfoxide is so hygroscopic that it readily moves through the skin, carrying many drugs with it. The vehicle may contain ingredients (e.g., Tween) intended to facilitate percutaneous drug absorption by altering the integrity of the stratum corneum. Disruption of the composition or lipid orientation of the stratum corneum enhances drug penetrability. A vehicle that hydrates the corneum facilitates drug penetration. Occlusion of the skin increases hydration; vehicles can occlude by preventing skin transpiration, the passage of water vapor from the skin. Occlusive bandages also can be used to facilitate drug absorption. Water associated with hydration alters the compact structure of the corneum, decreasing resistance to drug movement. Dehydration of the stratum corneum decreases drug absorption; rehydration might be indicated before drug application.

Other patient factors that influence drug movement include the integrity of the barrier presented by the stratum corneum. Drug absorption dramatically increases if the skin has been traumatized, such as might occur with rubbing a medicament vigorously onto the skin. Prior removal of debris on the surface of the skin (dirt, blood, and hair) can increase drug absorption, as can increasing the temperature of the skin (with sweats or water). Enhanced blood flow to the area might force drug into the hair follicles and through the stratum corneum. A warmer environmental temperature also might increase drug movement into the skin.

Many vehicles are represented in the commercial products for veterinary use. "Compounding" of dermatologic products is a relatively common practice in veterinary medicine. Although this can often provide a safe and effective therapeutic agent, one must keep in mind that the effect of the vehicle on bioavailability of the active ingredient(s) can be profound. The resulting product may be entirely ineffective due to lack of absorption, or it may cause toxicity as a result of systemic absorption.

Types of Vehicles

Water itself can be therapeutic. Bathing with water vehicles (especially shampoos) contributes to dermatologic therapy by removing debris, including potential allergens, bacteria, and other organisms, from the skin surface and rehydrating and cooling the skin (if cool water is used) (Kwochka, 1995a). The addition of other drugs (shampoos, soaks, and dips or rinses) to water, forming an aqueous solution, suspension, or lotion, can create other therapeutic effects. Aqueous medications are often the topical treatment of choice for acute exudative dermatoses.

Shampoos, a type of water vehicle, can be very effective adjuvants for the control of dermatoses (Kwochka, 1995a,b). In general, contact time should be at least 10 minutes. Shampoos generally are administered once to twice weekly. Examples of shampoos with therapeutic intent include hypoallergenic shampoos, which are cleansing and moisturizing; antipruritic shampoos, which often contain colloidal oatmeal along with antihistamines, anesthetics (pramoxine hydrochloride), or cortisone 1%; or insecticidal shampoos containing compounds such as pyrethrins, carbaryl, and permethrin. Application of rinses, sprays, or lotions can enhance the residual effect of shampoos.

Rinses generally are applied after a shampoo and are not necessarily intended to be completely rinsed from the coat. Incomplete rinses may increase the residual effect of the drug but also may leave the coat greasy feeling and dull (especially long-haired coats). Rinses include cream rinses (generally rinsed off the animal) and aqueous rinses (generally not rinsed off). Aqueous rinses also can be applied as a soak, which should last at least 10 to 15 minutes. Powders intended to be applied as soaks can be placed in cheesecloth or nylon stockings before placement in water.

Lotions are liquid or semiliquid combinations of active ingredient with a water, alcohol, glycerin, or propylene glycol base. Often the liquid base evaporates, and a thin film of powder remains on the skin. For this reason, lotions may have a drying effect on the skin. Examples include calamine lotion and conofite lotion (antifungal). Lotions also are available with a variety of antipruritic and parasitic medications.

Both aerosol and pump sprays are available for many veterinary products. Those with alcohol bases may be drying to the target area. Animals may need to be clipped to facilitate penetration of the hair coat. Foams consist of a mixture of finely divided gas bubbles interspersed in a liquid. These preparations provide an effective way of spreading a small amount of liquid over a large surface area. A potential drawback is the noise of the application, which may frighten the patient. Both sprays and lotions may be easier to use than creams and ointments, especially for dogs with long hair coats.

Creams and ointments are mixtures of grease or oil and water that are blended together into an emulsion. In general, ointments are greasy to the touch and form an occlusive layer over the skin, reducing water loss. Creams are smooth to the touch and, once applied to the skin, are rapidly absorbed or evaporate (i.e., there is no occlusive layer left on the surface of the skin). In general, creams and ointments are contraindicated in exudative areas. Examples include triple antibiotic ointments and creams and hydrocortisone ointments and creams. Hydrocarbon bases are emollient, being composed of vegetable oils and animal fats. Examples include oleic acid, paraffin, petrolatum, and wax. They generally are hydrophobic and occlusive, causing the stratum corneum to hydrate. They are greasy, however, and cannot be washed off. Anhydrous absorption bases contain little to no water but readily accept large amounts of water while maintaining a thick consistency. Examples include hydrophilic petrolatum and anhydrous lanolin.

Emulsions are oil and water combinations. Water-oil emulsion bases are water-washable bases that are easily removed from the skin surface. The oil phase generally is petrolatum with an alcohol; the aqueous phase may be water, propylene glycol, polyethylene glycol, or glycerin. Oil-water emulsion bases are composed of an aqueous phase that is greater than the oil component. These tend to be water washable, nongreasy, and nonocclusive. Finally, water-soluble-based ointments have no hydrophobic lipid base. They are completely water soluble, do not hydrolyze, and do not support the growth of microorganism contaminants in the product. If the preparation is in a gelled medium, the product is a gel (e.g., a combination of propylene glycol, propylene gallate, methylcellulose, polyethylene glycol, and others). Dimethylsulfoxide is commonly prepared as a gel (Riviere and Spoo, 1995). Gels are clear, colorless, and water miscible. Gels are becoming more popular because they can be rubbed into the skin to completely disappear and do not leave a sticky feeling. Examples of gels in veterinary medicine are Oxydex and Pyoben.

Dimethylsulfoxide (DMSO) has the ability to allow some substances ordinarily unable to penetrate the skin to be carried through it. Dimethylsulfoxide is a waste product of wood processing that has been used in a large number of topical medicaments. In addition to its hydrophilic actions, DMSO is characterized by bacteriostatic, anti-inflammatory, fibrinolytic, and vasodilatory actions. Topical analgesia may reflect a thermal affect, which occurs with direct application (Riviere and Spoo, 1995). At concentrations greater than 70%, however, DMSO can cause skin irritation. In concentrations greater than 50%, DMSO has been shown to enhance the percutaneous absorption of a large number of drugs, including glucocorticoids, antibiotics, hormones, and anti-inflammatories. Absorption increases as DMSO concentration reaches 100% (Riviere and Spoo, 1995). Dimethylsulfoxide increases percutaneous absorption of fluocinolone (a potent glucocorticoid) by a factor of five and other compounds by as much as a factor of 25. Dimethylsulfoxide is only approved for use in the horse (for traumatic musculoskeletal injuries) and the dog (in Synotic, a commercial ear preparation). Any other use for DMSO is considered extralabel use. Toxic effects that should be considered when DMSO is used include teratogenicity (contraindicated in pregnant animals), potential for inducing degranulation of mast cells in underlying skin, and, in cats, hemolysis with hemoglobinuria and methemoglobinuria. Dimethylsulfoxide has been shown to induce lenticular changes in animals and humans. Gloves should be worn when DMSO is handled.

Adsorbents act to bind potentially noxious agents, keeping them from damaging the skin. Protectants provide an occlusive layer that physically protects the skin from the external environment. Together, these two classes of vehicles are represented by dusting powders and mechanical protectives (kaolin, lanolin, mineral oil, petrolatum, zinc stearate). Dusting powders generally are inert, composed of starch, calcium carbonate, talc, titanium dioxide, zinc oxide, and boric acid. Smooth-surfaced powders prevent friction, protecting abraded and raw skin. Rough or porous powder surfaces absorb water, tending to occlude the skin surface when wetted. Rough powders should be avoided on moist or exudative lesions because of the risk of secondary bacterial or fungal infections. Care should be taken to make sure that powders, and in particular talc, are not used within a body cavity because of the potential for a massive granulomatous response.

Demulcents are high-molecular-weight water-soluble compounds that reduce irritation. They, like protectants, can coat the surface of damaged skin, protecting the stratum corneum and its underlying structures, and they inherently reduce irritation. Examples include mucilages, gums, dextrins, starches, methylcelluloses, and polyvinyl alcohol (Riviere and Spoo, 1995). Among those most commonly used in veterinary medicine are glycerin, propylene glycol, and polyethylene glycols. Glycerin, when used in high concentrations on the skin, can dehydrate and irritate it by increasing transepidermal water loss. Propylene glycol is miscible with water. Like glycerin, it is hygroscopic, is not occlusive, and also is bacteriostatic and fungistatic. As such it might be considered the "ideal" vehicle. It spreads easily on the skin surface, has a low evaporation rate, is not greasy, and may hydrate rather than dehydrate the skin (Riviere and Spoo, 1995). Topical hypersensitivity occurs occasionally. Several polyethylene glycols are available. They differ markedly in molecular weight, with the number directly correlating with size and viscosity. Polyethylene glycols that are 900 or above tend to be semihard to waxy solids at room temperature; lower molecular weight products are liquid. These compounds are not easily hydrolyzed but are very water soluble and nontoxic (Riviere and Spoo, 1995).

Astringents cause precipitation of proteins and prevent exudation. Because of their inability to penetrate the skin, their action is predominantly on the surface. Many astringents are also antiseptic. Astringents can arrest hemorrhage by coagulating plasma proteins (ferric chloride, silver nitrate). Burow's solution is available commercially as Domeboro (aluminum acetate powder or tablets) for use as an astringent in exudative dermatoses. Magnesium sulfate (Epsom salt) is not an astringent but acts to dehydrate or "draw" water from the tissues.

Emollients are fatty or oleaginous substances that soften, protect, and soothe the skin. They are often used to make the cream or ointment vehicle in many dermatologic preparations. Examples include mineral oil, petrolatum, glycerin, and vegetable and animal oils. In veterinary medicine, emollients are used as rinses after baths. Most of these chemicals have a characteristic "medicinal" odor that appeals to owners.

Classes of Topical Drugs

Many topical products are commercially available (Table 33–1), and many have multiple effects. Some of these agents are also discussed in other chapters (e.g., those on parasitology, antibacterials, and antifungals).

Antiseborrheics

Antiseborrheic drugs include keratolytics and keratoplastics. The appropriate antiseborrheic depends on the patient's condition (seborrhea sicca vs. seborrhea oleosa).

Sulfur is keratolytic (keratolytics hydrate and soften the stratum corneum, promoting its mechanical removal) and keratoplastic (keratoplastics normalize keratinization). It has a mild follicular flushing action but is not a good degreaser. It also has antibacterial and antipruritic effects. Its keratolytic effects may reflect inflammation that ultimately causes sloughing of the stratum corneum. Keratoplastic effects probably reflect cytostatic effects (Riviere

Table 33–1. Selected Commercially Available Topical Dermatologic Products

Active Ingredient	Trade Name	Company Source
Glucocorticoids		
Betamethasone dipropionate, 0.05% cream, ointment	Diprolene	Schering
Betamethasone dipropionate, 0.05% ointment	Diprosone	Schering
Betamethasone valerate, 0.1% ointment	Valisone	Schering
Betamethasone valerate, 0.1% cream, lotion	Valisone	Schering
Clobetasol propionate, 0.05% cream, ointment	Temovate	Glaxo Derm
Desonide, 0.05% cream	Tridesilon	Miles
Desoximetasone, 0.25% cream, ointment	Topicort	Hoechst-Roussel
Diflorasone diacetate, 0.05% ointment	Psorcon	Dermik
Fluocinolone acetonide, 0.025% ointment, cream	Synalar	Syntex
Fluocinolone acetonide, 0.1% solution	Synotic	Syntex
Fluocinolone acetonide, 0.01% shampoo	FS Shampoo	Hill Dermaceuticals
Fluocinonide, 0.05%	Lidex	Dermik
Hydrocortisone, 1 and 2.5% cream, ointment	Hytone	Dermik
Hydrocortisone, 1% spray	Cortispray	DVM Pharmaceuticals
Hydrocortisone, 1% spray	Dermacool-HC	Allerderm/Virbac
Hydrocortisone, 1% solution	HB 101	Butler
Hydrocortisone, 1% spray	Hydro-Plus	Phoenix
Hydrocortisone, 1% spray	Hydro-10 Mist	Butler
Hydrocortisone, 1% spray	PID-HC	VRx
Triamcinolone acetonide, 0.5% cream	Kenalog	Westwood-Squibb
Triamcinolone acetonide, 0.1% cream, lotion	Kenalog	Westwood-Squibb
Triamcinolone acetonide, 0.1% cream	Vetalog	Solvay
Hypoallergenic Shampoos, Moisturizing		
Hypoallergenic moisturizing shampoo	Hylyt*efa	DVM Pharmaceuticals
Hypoallergenic moisturizing shampoo	Allergroom	Allerderm/Virbac
Hypoallergenic moisturizing shampoo	Mycodex	Pfizer Animal Health
Antiseborrheic		
Benzoyl peroxide (see antimicrobials)		
Benzoyl peroxide with sulfur	Sulf/oxydex	DVM Pharmaceuticals
Coal tar 2%	Clear Tar	Veterinary Prescription
Coal tar 3% (juniper tar with sulfur and salicylic acid)	Lytar	DVM Pharmaceuticals
Coal tar 4%	Allerseb-T	Allerderm/Virbac
Salicylic acid and sulfur	Sebalyt	DVM Pharmaceuticals
With tricolan, an antibacterial	Sebolux	Allerderm/Virbac
Without tricolan	Selsun Blue	Abbott
Selenium		
Antipruritic Shampoos		
Colloidal oatmeal	Epi-Soothe Shampoo	Allerderm/Virbac
Colloidal oatmeal with antihistamine diphenhydramine hydrochloride	Histacalm Shampoo	Allerderm/Virbac
Colloidal oatmeal with anesthetic agent pramoxine hydrochloride	Relief Shampoo	DVM Pharmaceuticals
Colloidal oatmeal with 1% hydrocortisone	Cortisoothe	Allerderm/Virbac
Colloidal oatmeal with synergized pyrethrins	Ecto-Soothe Shampoo	Allerderm/Virbac
Colloidal oatmeal with carbaryl	Ecto-Soothe Carbaryl Shampoo	Allerderm/Virbac
Colloidal oatmeal with synergized pyrethrins and permethrin	Synerkyl Pet Shampoo	DVM Pharmaceuticals
Ethyl lactate	Etiderm	Allerderm/Virbac
Rinses		
20% colloidal oatmeal	Epi-Soothe Cream Rinse and Conditioner	Allerderm/Virbac
20% colloidal oatmeal with 1% pramoxine hydrochloride	Relief Creme Rinse	DVM Pharmaceuticals
Colloidal oatmeal	Epi-Soothe Bath Treatment	Allerderm/Virbac
Oilated oatmeal with 43% colloidal oatmeal and mineral oil	Aveeno Oilated Oatmeal	Rydelle
Moisturizing bath oil with essential fatty acids	Hylyt*efa Bath Oil/Coat Conditioner	DVM Pharmaceuticals
Moisturizing bath oil	Alpha-Sesame Oil Dry Skin Rinse	Veterinary Prescription
Humectant	Humilac	Allerderm/Virbac
Sprays and Lotions		
Antipruritic lotion	Relief Lotion	DVM Pharmaceuticals
Hamamelis extract, menthol, colloidal oatmeal, and lidocaine	Dermacool with Lidocaine Spray	Allerderm/Virbac
2% Diphenhydramine hydrochloride	Histacalm Spray	Allerderm/Virbac
Colloidal oatmeal and 1% pramoxine hydrochloride	Relief Spray and Relief Lotion	DVM Pharmaceuticals
2% Benzyl alcohol, 0.05% benzalkonium chloride, and hamamelis distillate	PTD Lotion	Veterinary Prescription
0.1% Triamcinolone, 0.025% fluocinolone, 0.1% betamethasone		
0.5%–2.5% Hydrocortisone	Cortispray Dermacool-HC	DVM Pharmaceuticals Allerderm/Virbac
Hydrocortisone lotion	Corticalm PTD-HC	DVM Pharmaceuticals Veterinary Prescription

Table 33–1. Selected Commercially Available Topical Dermatologic Products *(Continued)*

Active Ingredient	Trade Name	Company Source
Antimicrobials		
Benzoyl peroxide shampoo	Oxydex Shampoo	DVM Pharmaceuticals
Benzoyl peroxide shampoo	Sulf/oxydex Shampoo	DVM Pharmaceuticals
Benzoyl peroxide shampoo	Pyoben Shampoo	Allerderm/Virbac
Benzoyl peroxide shampoo	Mycodex Benzoyl Peroxide Shampoo	Pfizer Animal Health
Chlorhexidine	Chlorhexiderm Shampoo	DVM Pharmaceuticals
	Nolvasan Shampoo	Fort Dodge
	Nizoral Shampoo	Janssen Pharmaceutica
Miconazole lotion	Conofite Lotion	Mallinckrodt Veterinary
Miconazole cream	Conofite Cream	Mallinckrodt Veterinary
2% Miconazole and 0.5% chlorhexidine shampoo	Dermazole Shampoo	Allerderm/Virbac
2.5% Selenium sulfide	Selsun Rx 2.5% Selenium Sulfide Lotion	Ross
Chlorhexidine 0.5% and 1%		
Enilconazole	Imaverol	Janssen Pharmaceutica
Lime sulfur 2% solution	Lymdyp	DVM Pharmaceuticals

and Spoo, 1995). Sulfur also has a mild follicular flushing action. Commercially available products containing sulfur include Sebbafon, Lytar, Mycodex Tar & Sulfur, ADAMS Sulfur Shampoo, and ALLERSEB-T.

Salicylic acid is keratoplastic, bacteriostatic, and mildly antipruritic. It is frequently used in combination with sulfur products, including most of the sulfur products listed earlier. When salicylic acid is combined with sulfur, a synergistic effect results. In stronger concentrations (6%), it acts as a keratolytic.

Coal tar is keratolytic and keratoplastic and has some degreasing action. It is also frequently used in combination with sulfur and salicylic acid. Commercial shampoos are frequently used in veterinary medicine and include Lytar, Allerseb-T, and Mycodex Tar & Sulfur. Straight tar lotions should not be used in veterinary medicine, especially with cats. Coal tar preparations are potentially irritating, photosensitizing, carcinogenic, and staining.

Benzoyl peroxide (2% to 5%) is keratolytic, bactericidal, degreasing, and follicular flushing. It also is a strong oxidizer, free radical generator (hence, is antibacterial), and antimicrobial (Riviere and Spoo, 1995). Benzoyl peroxide is metabolized by viable epidermal cells in the skin to benzoic acid. In high concentrations, it can irritate the skin. It may be too drying for some patients with seborrhea sicca. Commercial products available for veterinary patients include Oxydex and Pyoben shampoos. A gel form of 5% is available for veterinary use, primarily for treatment of chin acne (Messinger, 1995). Other uses include fold pyodermas and local superficial or deep pyodermas.

Resorcinol is a keratolytic agent also with bactericidal and fungicidal effects. It is a protein precipitant that promotes keratin hydration, acting as a keratolytic (Riviere and Spoo, 1995). It often is combined with another keratolytic (e.g., sulfur, salicylic acid) (Riviere and Spoo, 1995).

Selenium sulfide is antiseborrheic, keratolytic, and keratoplastic by virtue of its antimitotic effects. Cell proliferation and sebum formation are slowed. It tends to be irritating, however, and can stain hair. Mucous membrane irritation may occur if accidental contact occurs. A product for humans is Selsun Blue. Fatty acids (e.g., undecylenic acid [Desenex]) are also keratolytic.

Retinoids

Retinoids are natural or synthetic derivatives of retinol (vitamin A) that exhibit vitamin A activity (Fig. 33–1) (Guzzo et al., 1995). Dermatologic effects of vitamin A include epithelial differentiation. Vitamin A deficiency causes metaplasia of glandular epithelia; excessive vitamin A causes keratinizing epithelia to differentiate into a secretory epithelia (Power and Ihrke, 1990). The antikeratinizing effects are the target of drug therapy (Power and Ihrke, 1990). Retinoids tend to "normalize" the skin. Although natural retinoids have proved to be too toxic for clinical use, the synthetic products are characterized by specific effectiveness with decreased toxicity. They tend to vary in bioavailability, in metabolism to active versus inactive metabolites, and in tissue distribution patterns. First-generation compounds include retinol and its derivatives tretinoin and isotretinoin. The second-generation products are synthetic and include etretinate and acitretin, approved for treatment of acne and psoriasis, respectively. The third-

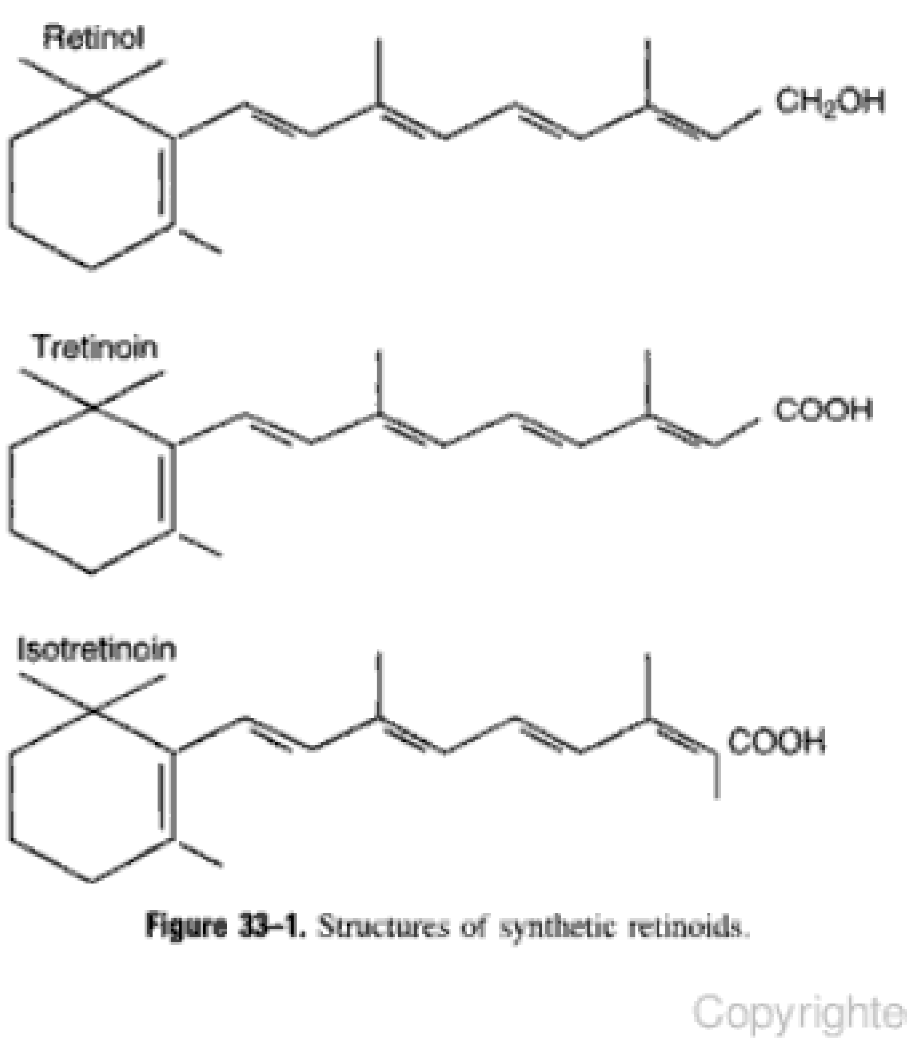

Figure 33–1. Structures of synthetic retinoids.

generation compounds, arytenoids, are in development (Guzzo et al., 1995).

The effects of the retinoids include cellular proliferation and differentiation, immunomodulation, inflammation, and production of sebum. Their actions are mediated by retinoic acid receptors, members of the thyroid/steroid receptors (Guzzo et al., 1995). Retinoids may influence genomic expression of cells by altering RNA synthesis, typical of other steroids. Tretinoin increases dermal thickness and granular layer thickness, decreases melanocytic activity, and increases the secretion of a polysulfated glycosaminoglycan intercellular matrix. In people, wrinkling is reduced. It is formulated as a 0.01% to 0.1% topical preparation. Therapy begins with lower concentrations and gradually increases. Adverse effects include erythema, peeling, burning, and stinging, which tend to decrease with time and are less likely to occur when the drug is prepared as an emollient.

Isotretinoin normalizes keratinization of the follicular epithelium and reduces sebum synthesis and, in humans, *Proprionobacterium acnes.* It is administered orally, however, with cumulative doses being important to efficacy. Toxicity is manifested in the skin and mucous membranes, is dose dependent, and, in humans, may facilitate the growth of *Staphylococcus aureus.* Dermatologic manifestations include epistaxis, dry eyes, blepharoconjunctivitis, erythematous eruptions, and dry mucous membranes (Guzzo et al., 1995). Systemic manifestations can be minimized with short-term therapy and include increased liver enzymes, myalgia, and arthralgia. Teratogenicity occurs with all retinoids; the drugs generally are contraindicated in pregnancy. Isotretinoin was studied in dogs (Kwochka, 1989). Four of 29 developed conjunctivitis, which resolved once therapy was discontinued. Cats may have a higher incidence of side effects, including periocular erythema, epiphora, and blepharospasm. The potential veterinary applications of isotretinoin include selected abnormalities of sebum production such as primary idiopathic seborrhea and comedo syndromes.

Etretinate is a synthetic aromatic retinoid that is effective for the treatment of inflammatory psoriasis. The arotinoids are highly potent aromatic analogs of retinoic acid and represent the third generation. It is extremely lipophilic and is stored in adipose tissue. Accumulation is sufficient to allow detection of the drug in people 2 to 3 years after its use is discontinued. It normalizes keratin expression in epidermal cells, suppresses chemotaxis, decreases stratum corneum cohesiveness, and may impair cytokine function (Guzzo et al., 1995). It is less likely than isotretinoin to cause conjunctivitis, but hair loss, cutaneous exfoliation, bruising, and liver dysfunction are more common. Collection of a baseline minimum database is recommended for people before its use. Its teratogenicity precludes use by women of childbearing age; owners of animals using the drug should be warned of its contraindications (Guzzo et al., 1995). The drug may no longer be available because of its adverse effects.

The use of retinoids in clinical veterinary medicine has not been well established. Animals are not afflicted by skin diseases typical of those for which retinoids are indicated in human patients (e.g., psoriasis acne). Use is limited by lack of known effects and indications, cost, and the risk of side effects. Dogs, however, appear to be more tolerant of the retinoids than humans (Power and Ihrke, 1995; Kwochka, 1989). Side effects that have been reported in dogs include inappetance, vomiting, diarrhea, thirst, pruritis, conjunctivitis, chelitis, stiffness, and hyperactivity (Power and Ihrke, 1995). Keratoconjunctivitis has been reported in dogs (Power and Ihrke, 1995; Kwochka, 1989). Tear composition is changed, leading to more rapid evaporation. Schirmer's tear test should be monitored monthly for the first 6 months of therapy. Clinical pathology changes are rare, but monitoring before and 30 days after the start of therapy is recommended for dogs receiving synthethetic retinoid therapy (Power and Ihrke, 1995). In cats, the most common side effect is anorexia. Teratogenicity is a likely problem, particularly with etretinate, when used for intact females.

The most common use of synthetic retinoids in dogs has been for treatment of keratinization disorders of dogs, particularly primary seborrhea of cocker spaniels. Etretinate has been evaluated in spaniels with idiopathic seborrheic dermatitis (approximately 10 mg or 0.75 to 1 mg/kg per day orally). Animals generally respond well with a decrease in scaling, a softening and thinning of seborrheic plaques, decreased pruritis, and reduction in odor. Response occurs within 2 months and improvement continues for at least 2 more months (Power and Ihrke, 1995). The more severe the syndrome, the slower the time to response; discontinuation of therapy is likely to result in recrudescence of clinical signs within 3 to 12 weeks (Power and Ihrke, 1990). The drug was minimally effective in the treatment of ceruminous otitis associated with seborrhea (Power and Ihrke, 1995). Maintenance therapy ranges from 10 mg every other day to 10 mg daily, alternating 30 days on and 30 days off. Isotretinoin (1 and 3 mg/kg per day) appears to be much less effective (Powers and Ihrke, 1990). Neither isotretinoin nor etretinate has proved to be effective in West Highland white terriers, and etretinate was ineffective in basset hounds. Both etretinate and isotretinoin have proved effective in the treatment of schnauzer comedo syndrome (Power and Ihrke, 1990, 1995) and canine ichthyosis. Newer applications of the synthetic retinoids include hair follicle dysplasia (etretinate), which should respond in approximately 30 days, and selected dermatologic cancers. These include solar-induced squamous cell carcinoma (etretinate 2 mg/kg divided or once daily for 6 months), mycosis fungoides (etretinate or isotretinoin 3 to 4 mg/kg divided or once daily), and selected benign cutaneous neoplasms (multiple sebacelous adenomas, epidermal cysts, inverted papillomas, and infundibular keratinizing acanthomas) (Power and Ihrke, 1995).

Isotretinoin for the treatment of disorders of the sebaceous glands has been variably successful; success may be breed dependent. It was proved effective in sebaceous adenitis of standard poodles in one study but ineffective in another (Power and Ihrke, 1990). A higher dose (2 to 3 mg/kg) has been recommended. Hair growth in poodles that do respond is abnormal, however, in that kinks are lost. Vizslas appear to respond to isotretinoin very well (Power and Ihrke, 1990). In contrast, neither isotretinoin nor etretinate appears to be effective in sebaceous adenitis of Akitas.

Retinoids appear to be safe for cats but do not appear

0.15% flea sprays but also up to 65% as spot tick products. Chlorinated hydrocarbons should not be used (if there happens to be any still on the market). There are two types of cholinesterase inhibitors available: carbamates and organophosphates.

Carbamates such as carbaryl are available in sprays, dips, collars, and premise-control sprays, and they are safe for dogs and cats. Toxicity of carbamates as well as organophosphates reflects overstimulation of the parasympathetic system and should be treated with atropine and 2-pyridine aldoxime methylchloride.

Organophosphates are the most toxic insecticides used in veterinary medicine. With one exception, these agents should not be used around cats. Care should be taken to avoid cumulative exposure if animals are exposed to this class of insecticide in lawn and garden preparations. Examples of commonly used organophosphates are chlorpyrifos (Dursban, Duratrol), used for flea sprays and dips; diazinon, used for environmental flea and tick control; malathion, used on both cats and dogs and often combined with other insecticides (noncholinesterase inhibitors); phosmet (Paramite Dip), useful for flea control but not effective for scabies; cythioate (Proban), a systemic insecticide; and fenthion (Pro-Spot), topically applied for a systemic effect.

Fipronil (Frontline) is a new synthetic molecule in the phenylpyrazole family. It acts at γ-aminobutyric acid (GABA) receptors and inhibits GABA-regulated chloride flux into the nerve cell. It is a flea adulticide and has efficacy against ticks. It may also be effective against scabies mites. Preliminary studies indicate good residual activity even after bathing. This product is available as an on-animal spray or as a spot-on product.

Imidacloprid (Advantage) is a spot-on application product that kills adult fleas. It works by preventing postsynaptic binding of acetylcholine, leading to respiratory paralysis of the flea. This product can be removed by bathing. Caustic burns and irritation can occur in cats. It must be applied every 30 days to be effective.

Amitraz (Mitaban) is a monoamine oxidase inhibitor. It is the only licensed product for treatment of demodicosis. Mitaban is also efficacious against scabies but is considered off-label use for scabies. This product rapidly oxidizes on exposure to light and air, and the breakdown product is more toxic than the parent compound. Mitaban should be mixed fresh each time, and the entire contents should be used to avoid toxicity. Side effects include sedation and lethargy (sometimes for 24 hours), pruritus, bradycardia, hypothermia, hypotension, and hyperglycemia. Amitraz should be avoided in epileptic dogs and in animals receiving behavior-modifying drugs. Yohimbine works as a reversing agent.

Ivermectin (Ivomec 1%) is a GABA agonist that leads to parasite paralysis. In mammals, GABA in the central nervous system is protected by the blood-brain barrier. Ivermectin is a large molecule that cannot pass the blood-brain barrier except in certain breeds. It is efficacious against scabies, lice, otodectes (ear mites), and cheyletiella. It is *not* approved for use in small animals for treatment of parasites other than as a heartworm preventive. Ivomec is rapidly absorbed orally or subcutaneously. The administration into the ear canal is not recommended. It should not be used in collies, border collies, shelties, Australian shepherds, Old English sheepdogs, or any dog that looks like a collie. Also, it is not recommended for any animal less than 12 weeks of age. Daily ivermectin has been used to treat demodicosis, but it is a treatment of last resort. Benzodiazepines are contraindicated for concurrent use. Treatment of ivermectin toxicity is symptomatic and supportive. There is no good antagonist available.

Milbemycin (Interceptor) has a similar action to ivermectin. Its use in dermatology is confined to daily oral administration for the treatment of refractory demodicosis. Therapy may take 6 to 9 months, and relapses are common. Cost is a limiting factor. This drug is not approved for use for demodex treatment. Although not contraindicated in collies and collie-like dogs, caution is advised for side effects.

Flea insect growth regulators (IGRs) are endogenous chemicals in insects that control the early stages of their metabolism, morphogenesis, and reproduction. Synthetic compounds mimic the effects of the natural chemicals. By maintaining high levels during maturation and pulpation of larvae, insects are prevented from developing. Natural levels decrease over time and allow normal maturation. These products have no effects on mammals and are very safe. They are often combined with pyrethrins or pyrethroids to increase the spectrum of activity to include adults. Several products are available: Methoprene (Ovitrol) is a juvenile hormone analogue available for on-animal and environmental use. It is degraded by ultraviolet light and hormone esterase. Fenoxycarb (Basis) is a juvenile hormone mimetic that is not degraded by light or hormone esterase. It was recently discontinued, however, due to evidence of carcinogenesis in laboratory animals. Pyriproxifen (Nylar) is similar to fenoxycarb and is the newest product on the market. Preliminary studies indicate very long residual activity even when the animal is bathed and excellent environmental stability.

Lufenuron (Program) is a benzoylphenylurea that inhibits synthesis and deposition of chitin within the ova and larval exoskeleton of developing fleas. It is strongly lipophilic and stored in adipose tissue with slow release into the blood vasculature, providing long residual activity from a single dose. It does not affect adults or the amounts of egg, pupae, or vertebrate production. Because of the slow absorption from the gastrointestinal tract, this product is given with food. Cats do not absorb this product as well as dogs, and therefore a higher dosage on a per pound basis is needed for the same efficacy and duration of effect. This product is very safe and carries no contraindications.

Miscellaneous

Pennyroyal oil is a volatile oil extracted from plants in the mint family. Due to its limited efficacy and evidence of hepatotoxicity, this product is not recommended. D-limonene is from oils of citrus fruits. Toxicities have been noted in the cat, especially depression, ataxia, and toxic epidermal necrolysis. This product is not recommended. Tea-tree oil contains various monoterpenes. Toxicities with this oil have been reported, and there is no scientific evidence to support claims of its efficacy.

SYSTEMIC DERMATOLOGIC THERAPY

Systemic dermatologic therapy is indicated for diffuse, serious, or chronic conditions (Table 33–2).

Antimicrobials

Antimicrobials indicated for the treatment of dermatologic disorders are discussed in Chapters 10 and 11. A number of antimicrobials are effective for the treatment of bacterial skin diseases (pyoderma). Among them, care should be taken when using sulfonamides, often selected as first choice, because of their ability to suppress the synthesis of thyroid hormones (see Chapter 32). A study in 20 dogs receiving sulfamethoxazole (with trimethoprim) at 30 mg/kg every 12 hours for 6 weeks found marked suppression of thyronine concentrations and response to thyroid-stimulating hormone. Suppression did not occur with 15 mg/kg of sulfadiazine (trimethoprim) once daily for 4 weeks (Hall and Campbell, 1995). Thyroid function returned to normal within 3 weeks of discontinuing therapy. Suppression may result from inhibition of thyroid peroxidase by the amino group in the sulfonamide. The effect of sulfonamides on feline thyroid function have not been reported.

Anti-Inflammatory/Antipruritic Agents

Glucocorticoids

Glucocorticoids are discussed in Chapter 17 and other immunomodulators in Chapter 19. Glucocorticoids continue to be overused and abused for treatment of dermatologic diseases (Scott, 1995a; Kunkle, 1995). Scott (1995a) notes that over 50% of his referral cases are complicated by the excessive use of the drugs. Yet, glucocorticoids remain an important and legitimate component of both acute and chronic treatment of a variety of skin diseases associated with pruritus or inflammation resulting from allergic diseases (atopy, flea bite or other insect- and arachnid-mediated hypersensitivity, food hypersensitivity, contact dermatitis), pyotraumatic dermatitis ("hot spots"), and acral lick dermatitis (Scott, 1995a). Note that glucocorticoids for acral lick dermatitis may largely be replaced with behavior-modifying drugs for this syndrome. Glucocorticoids also remain the cornerstone of therapy for many of the autoimmune diseases affecting the skin, including the eosinophilic granuloma complex, pemphigus complex, systemic lupus erythematosus, and discoid lupus erythematosus. Optimal therapy of each of these diseases varies, as some may respond to glucocorticoids alone and some may require a combination of glucocorticoids and alternate immunosuppressive drugs such as azathioprine or cyclophosphamide. Routes of administration will vary with lesion and intent and include topical, intralesional, and systemic (intravenous, subcutaneous, intramuscular). The use of topical glucocorticoids was previously discussed; note that side effects of glucocorticoids will not necessarily be avoided by limiting therapy to topical application. In general, oral administration is preferred for its convenience and ability to regulate dosage safely (including rapid withdrawal relative to other routes). Although some animals may appear to respond better to injectable rather than to oral drugs, differences in responses may reflect an insufficient oral dose. This is particularly likely to occur if the oral drug is one that is less potent than the injectable drug (Scott, 1995a).

The choice of glucocorticoid should be based on desired potency (e.g., dexamethasone is more potent than prednisolone and may be preferred for acute needs) balanced with a need to avoid side effects (prednisolone is characterized by a smaller tendency to negatively impact the hypothalamic-pituitary-adrenal axis; see Chapter 17) (Kunkle, 1995). Personal preference among clinicians ultimately also will determine the selection of specific drugs: Whereas prednisolone may be efficacious for some situations, it may not be for others. In addition, an animal may develop intolerable side effects to one glucocorticoid but not another. The development of steroid tachyphylaxis may lead to deselection of a steroid that previously was efficacious (Scott, 1995a). Remission in the case of acute exacerbation of clinical signs might respond to a "pulse dose" approach using the original anti-inflammatory dose (Kunkle, 1995).

Dermatologic conditions requiring glucocorticoid therapy range from mild to serious. Dermatoses associated with life-threatening conditions generally are limited to diseases that also are accompanied by diseases of multiple organs (e.g., immune-mediated disease). In such cases, glucocorticoid therapy should be aggressive, with doses sufficiently high to control disease. Regardless of the indication of glucocorticoids, alternate-day therapy should be a goal of maintenance (Kunkle, 1995). Not all conditions will, however, be sufficiently controlled with alternate-day therapy (Scott, 1995a). Because high doses of glucocorticoids are often required to adequately treat immune-mediated diseases, adverse effects are likely to occur. Concurrent administration of additional immunosuppressive drugs (azathioprine, cyclophosphamide, danazol) may allow the glucocorticoid dose to be decreased. Dose reduction for patients with autoimmune diseases should be conducted gradually and should occur for at least 2 weeks (longer if time to clinical remission was prolonged), and the actual dose should be decreased by no more than half. Clinical re-assessment should continue until a minimally effective dose is established for maintenance therapy.

Chronic inflammatory disorders (e.g., atopy or flea allergy dermatitis) should be treated less aggressively. A minimum effective dose should be determined by trial and error and re-evaluated such that the dose is reduced when possible. Agents that are amenable to alternate-day administration include the first-choice drugs prednisone and prednisolone and the second-choice methylprednisolone (Kunkle, 1995). The ideal alternate-day dose for these drugs is 0.22 to 0.55 mg/kg (Kunkle, 1995). The durations of action of hydrocortisone and cortisone may be too short for effective alternate-day therapy. Although triamcinolone's duration of anti-inflammatory action is similar to that of prednisolone and methylprednisolone, suppression of the hypothalamic-pituitary-adrenal axis is more likely but less typical of the long-acting agents such as dexamethasone and betamethasone.

All patients receiving glucocorticoids should be monitored, with physical examinations occurring at least twice

animals. The metabolite, however, causes rapid hemolysis. Cimetidine can be used to minimize toxicity by competing for drug-metabolizing enzymes (Guzzo et al., 1995).

Antihistamines

Despite structural differences, all classes of H_1 antihistamines have similar anti-inflammatory and side effects. The primary mechanism of action of these drugs reflects competitive inhibition of histamine at the receptor. Newer H_1 antagonists also block histamine release and have proved effective for treatment of atopy in humans (see discussion of antihistamines in Chapter 31). Differences in response among drugs, species, or disorders, might also, however, reflect impaired histamine release from mast cells or altered T-cell function. Side effects of these drugs also vary with the product and include gastrointestinal upset and neurologic manifestations, including drowsiness (the most common side effect) and hyperexcitability. Contraindications include central nervous system disorders (including epilepsy), glaucoma, and smooth muscle motility disorders such as might occur in the gastrointestinal or urinary tract. These products are generally used safely in human pregnancy, although safety has not been established in the pregnant or nursing cat and dog. Products with antihistamine activity only generally have fewer contraindications; the particular product should be reviewed before use and those with other pharmacologic effects avoided when appropriate.

Antihistaminergics can be beneficial in some cases of pruritis in dogs and cats. Because of varying effects among the drugs, each antihistaminergic should be tried for at least 1 week before an alternative medication is sought. Among the drugs tested in clinical trials, clemastine appears to be the most effective in stopping itching associated with pruritis in dogs and cats and is the antihistamine of choice (Logas, 1995). Cost can, however, be prohibitive; chlorpheniramine should be considered next for both dogs and cats (Messinger, 1995). The bitter taste of chlorpheniramine might be avoided by use of time-release capsules, which only need be administered once daily. Diphenhydramine and hydroxyzine may be less efficacious; in addition, hyperexcitability may limit use in cats. A minimally effective dose may reduce the incidence of side effects. Terfenadine, a second-generation antihistamine a recently approved for human use, is characterized by too many side effects (Logas, 1995). Acute toxicosis has been reported at 6.6 mg/kg, although most toxicities occur only at 30 mg/kg or more (Logas, 1995). Astemizole is another recently approved human product. Although it appears safe (1 mg/kg), its efficacy has not been established in animals. In human medicine, a combination of H_1 (the traditional antihistaminergic selection) and H_2 blockers has been recommended. The immunomodulating effects of H_2 blockers may benefit the dermatologic patient (Guzzo et al., 1995). Newer H_1 blocking drugs (terfenadine, loratadine) do not cause anticholinergic effects and are not sedating. Caution should be taken when combining these products with H_2 receptors, however, because of an increased risk of cardiac arrhythmias, probably due to inhibition of drug-metabolizing enzymes (Guzzo et al., 1995). Antihistamines may act synergistically with misoprostol in controlling pruritus; studies currently are under way.

Omega-3 (Omega-6) Polyunsaturated Fatty Acids

Body fats are stored as either adipose tissue or structural fat. Adipose tissue is rich in triglycerides, which are composed of a glycerol backbone and three fatty acids. Structural fats are represented by phospholipids, also composed of a glycerol backbone, two fatty acids (at the 1 and 2 positions), and a phosphate group (at the 3 position). Fatty acids can be released from glycerol by phospholipase. Saturated fatty acids have no double bonds. Unsaturated fatty acids (UFAs) include monunsaturated fatty acids, which have one double bond, and polyunsaturated fatty acids (PUFAs), which have two or more double bonds. The shorthand identification system of PUFA reflects the number of carbon atoms, the number (n) of double bonds, and the position of the first double bond from the terminal or omega methyl group end of the molecule (White, 1995). For example, the formula for linoleic acid, an essential fatty acid for mammals, is 18:2n-6; it contains 18 carbons and two double bonds, with the first double bond located between the sixth and seventh carbon. α-Linolenic acid (ALA) (18:3n-3) also contains 18 carbons but has three double bonds, with the first located between the third and fourth carbon (Fig. 33–2).

Essential fatty acids (EFAs) are those fatty acids required for normal physiologic function but cannot be synthesized by the animal and thus must be obtained in the diet (White, 1995). Among the functions of EFA are serving as a structural component of cell membranes primarily as arachidonic acid and in specialized tissues (retina and brain) as eicosapentaenoic acid (EPA) and docosahexaenoic acid (White, 1995). The PUFA component is important to determining fluidity of the membrane, rendering it more stable, and maintaining cellular permeability. The epidermal water barrier of the skin depends on linoleic acid lipids located in the intercellular lamellar granules at the level of the stratum granulosum/corneum interface. Essential fatty acids are also the source of eicosanoids, from which are derived prostaglandins, leukotrienes, platelet-activating factor, and related compounds. Prostaglandins are notable for their protective effects in many body systems; both classes of eicosanoids also are potent inflammagens (see Chapter 16).

Two families of UFAs are essential for mammals (see Fig. 33–2). Fatty acids of the n-3 (omega-3) series include ALA; EPA (20:5n-3) is a metabolic product of ALA found in fish oil. Fatty acids of the n-6 (omega-6) family include linoleic acid (LA), the precursor to arachidonic acid (AA), a fundamental component of cell membranes and thus the most important of the EFA in mammals (White, 1995). Gamma-linolenic acid (GLA) is a product of linoleic acid found in certain plant oils. It is elongated to dihomogamma linolenic acid, which is then converted to AA. Of the omega-3 series, ALA is elongated to EPA and then docosahexanoic acid (DHA) (Fig. 33–2). Because of the absence of microsomal desaturase enzymes necessary to make double bonds, mammals are unable to synthesize LA and ALA (White, 1995). Most mammals are, however, able to synthesize arachidonic acid from dietary sources of linoleic

inhibitory neurotransmitter GABA at peripheral neuronal synapses, resulting in paralysis and death of the parasite (see Chapter 15). Selective activity in animals reflects a difference in the peripheral role (nematodes and arthropods) versus central role (mammals) of this neurotransmitter. In most mammals, ivermectin does not penetrate the blood-brain barrier in sufficient concentrations to cause side effects. The drug is administered orally and parenterally; up to 3 weeks may elapse before the drug is totally eliminated in feces. The primary indication for ivermectin in small animals is mite infestation: feline and canine scabies, cheyletiellosis, and ear mites. The drug has also been used for mite infestations of guinea pigs and birds. Although clinical response may occur in several weeks, animals may remain skin-scrape positive for several to many months. Adverse reactions are idiosyncratic and have been reported primarily in herding breeds (collies, Shetland sheepdogs, Old English sheepdogs, Australian shepherds). Reactions have ranged from mydriasis, to tremors, ataxia, coma, and death. Ivermectin is contraindicated for such breeds. The 1% bovine product has been diluted with propylene glycol to allow more accurate dosing in small animals.

Milbemycin

Like ivermectin, milbemycin (twice the monthly heartworm preventive dose given daily) is effective for the treatment of demodectic mange. Response to treatment is lengthy. Also like ivermectin, milbemycin can cause toxicity, particularly in collie-type dogs, although this drug is slightly safer than ivermectin. Moxidectin also may be efficacious; collies also appear to be more sensitive to its adverse effects.

Immunomodulators

Immunomodulators (biologic response modifiers) potentiate some facet of the immune response (see Chapter 19). Many compounds described as immunomodulators have been used to treat a variety of dermatologic conditions. Immunosuppressants used to treat immune-mediated dermatologic disorders include glucocorticoids, cytotoxic (antineoplastic) drugs, and selected hormones. Immunostimulants tend to be less effective (see Chapter 19).

Staphylococcus aureus phage lysate (Staphage Lysate) is a vaccine containing parts of *S. aureus*, a bacteriophage, and culture medium ingredients. It is indicated for treatment of canine staphylococcal pyoderma. Vaccination is intended to result in stimulation of antibacterial antibodies. There may also be a hyposensitizing effect. Concomitant antimicrobial therapy should be used for the initial 4 to 6 weeks. Staphage Lysate is administered subcutaneously once a week initially, and then the dosage interval is lengthened. The vaccine is relatively expensive. Possible side effects include allergic reactions and local redness and swelling at the injection site. This vaccine should be reserved for patients with recurrent staphylococcal pyoderma that responds to antimicrobial therapy but relapses when therapy is discontinued. It is extremely important that other causes of pyoderma (allergies, ectoparasites, endocrinopathies) are identified and treated.

Propionibacterium acnes killed suspension (Immunoregulin) is available as an adjunct to antimicrobial therapy in the treatment of canine pyoderma. It has been shown to induce cell-mediated immunity. This bacterium is the species associated with human acne. Treatment with Immunoregulin involves intravenous injections twice weekly initially and then once weekly. Potential adverse effects include anaphylactic reactions. Disadvantages include expense and the need for intravenous injections (client cannot administer at home). It is the author's opinion that use of this agent should be reserved for patients failing all other forms of therapy.

Hyposensitization involves parenteral administration of allergens (antigens) in allergic patients. Although the mechanism of action of this therapy is unknown, the most appealing theory is that repeated exposure to the allergen may result in reduced cellular sensitivity (tolerance).

TRANSDERMAL DELIVERY OF DRUGS

Most drugs in human and veterinary medicine that are applied to the skin are intended to provide their pharmacologic effect where they are applied. Systemic absorption is intended to be minimal so that systemic effects will not be encountered. There are, however, a small number of drug products that are designed to be applied to the skin, absorbed transdermally, and attain high enough plasma concentrations to produce systemic effects. The same factors mentioned in the discussion of the principles of topical drug therapy affect drug absorption from cutaneous sites.

Transdermal drug delivery offers several advantages. It is easier to administer drugs transdermally, and drug delivery can be sustained, thus ensuring continued therapeutic effects. Drug input might be more precisely controlled over oral therapy because there are fewer factors complicating transdermal drug absorption such as first-pass hepatic metabolism.

Not all drugs may be administered transdermally. The drug should not be irritating to the skin and should be transdermally bioavailable. Effective transdermal drug delivery formulations are very difficult to design, which is probably why there are so few products available. Some products used in veterinary medicine, although not intended for transdermal absorption, can result in systemic absorption in the person treating the animal. Such drugs should be handled with nonpermeable gloves (i.e., DMSO, all anticancer drugs, nitroglycerin ointment, all antiparasitics [dips and shampoos], and altrenogest [Regu-mate]). Gloves might also be used when administering chloramphenicol, although percutaneous absorption in association with oral medication of small animals has not been documented.

Several products are used in veterinary medicine with the intent of achieving systemic therapeutic effects. Nitroglycerin ointment relaxes vascular smooth muscle primarily on the venous side and is used for dogs and cats to treat cardiogenic edema. The ointment is applied to glabrous areas (i.e., axillary, inguinal, or inside the ears). Onset of action is approximately 1 hour. Fenthion (Pro-Spot) and other systemic insecticides (discussed earlier) are applied topically. Scopolamine, nitroglycerin, and clonidine transdermal patches are available for use in human patients to treat motion sickness, angina, and hypertension, respectively. Fentanyl, a narcotic analgesic available in transdermal patches, has proved to be an effective and safe alternative to injectable opioid delivery for control of pain in dogs and cats (see Chapter 22).

TREATMENT OF SPECIFIC DERMATOLOGIC DISORDERS

Selected skin diseases are discussed in other chapters. Otitis externa, pyoderma, and other bacterial infections of the skin are discussed in Chapter 10. Fungal disorders are additionally discussed in Chapter 11, external parasites are additionally discussed in Chapter 15, immune-mediated diseases of the skin are discussed in Chapter 19, behavioral disorders of the skin are discussed in Chapter 25, and endocrinopathies affecting the skin are addressed in Chapter 32.

Chronic Pruritus

Pathophysiology

Pruritus is a cutaneous sensation that leads the animal to resolve the feeling by scratching, rubbing, licking, or chewing. The cause of the sensation is complex, as can be its resolution. Ideally, the underlying cause of the sensation is identified and treated, ultimately leading to resolution of the pruritus. Discussion of or even provision of a comprehensive list of the causes of pruritus is beyond the scope of this chapter.

Like pain, the sensation of pruritus consists of a peripheral signal, originating in the skin, and central perception, ending at the sensory cortex. A number of chemicals are responsible for signal generation and transmission in the skin, although which predominate in the dog and cat are not known. The chemicals largely are the same as those generating the inflammatory response and include both preformed chemicals (histamine, serotonin) and those synthesized in situ (prostaglandins, leukotrienes, proteases). The signal generated at the level of the skin can be modified by emotional, biochemical, or central factors, leading to behavior that appears to be disproportionate to the inciting cause (i.e., skin trauma induced in response to a single flea bite) (Miller, 1993). Drugs oriented toward control of pruritus can target either peripheral or central transmission. For chronic pruritus, drugs with systemic effects generally are more effective.

Drug Therapy

Topical Therapy

A number of nonglucocorticoid topical preparations may control pruritus (Scott, 1995a, Kwochka, 1995a). Care should be taken to select products that are not irritating or drying. Shampoos generally should be applied once to twice weekly. Cool water may be effective in some animals; antipruritic efficacy can be enhanced by the addition of moisturizing agents, colloids, anti-inflammatories, or anesthetics. Preparations that can be applied in "spots" include Caladryl lotion (composed of 1% diphenydramine, 8% calamine and camphor), Dermacool (hamamelis extract and menthol), and Histacalm (2% diphenhydramine) (Scott, 1995a).

Other medications available in sprays that might be helpful for control of pruritus include local anesthetics such as lidocaine (Dermacool) or promaxine (with colloidal oatmeal: Relief Spray), 2% benzyl alcohol with 0.05% benzalkonium chloride, and hamamelis distillate (PTD). In addition to anthistaminergic medications, sprays also may contain glucocorticoids for treatment of localized pruritis such as pyotraumatic pruritus and allergic pyodermatitis (Kwochka, 1995a). More potent sprays intended for acute management contain 0.1% triamcinolone, 0.025 fluocinolone, or 0.1% betamethasone; "milder" glucocorticoid sprays for long-term maintenance contain 0.5% to 2.5% hydrocortisone. Methosulfone, a metabolite of DMSO and thus an oxygen radical scavenger, can be diluted in water and applied topically as a spray. Sprays can be applied two to three times per day (Kwochka, 1995a). Sprays should be applied every 12 hours until inflammation and pruritis are controlled.

Glucocorticoid ointments and creams may be difficult to use because of lack of penetration through the haircoat into the skin. A hydrocortisone lotion that is not greasy or staining may be useful for treatment of large areas with some residual activity (Kwochka, 1995a).

Total body application of moisturizing and hypoallergenic shampoos, antihistaminergic shampoos (2% diphenhydramine), or colloidal soaks or shampoos with or without antihistamines, local anesthetics (Relief Shampoo), or hycrocortisone (Cortisoothe) are indicated for patients with generalized pruritus (Scott, 1995a; Kwochka, 1995b). Colloidal shampoos containing pyrethrins, carbaryl, or pyrethrins and permethrin will facilitate control of pruritus associated with fleas (Kwochka, 1995a). Application of a rinse, spray, or lotion after a shampoo will provide some residual effect (Kwochka, 1995a). Cream rinses containing colloidal oatmeal with (pramoxine) or without a local anesthetic are available for control of pruritus. Incomplete rinsing of a cream rinse may facilitate residual activity in dogs with short hair coats (coats of long hair become greasy). Antipruritic cream rinses might also be applied locally for control of localized pyoderma (e.g., RELIEF Lotion) (Kwochka, 1995a). Several aqueous rinses also are available for control of pruritus. These include 100% colloidal oatmeal (Epi-Soothe Bath Treatment), oilated oatmeal with 43% colloid (Aveeno Oilated Bath) (for very dry skin and haircoats, also applied as a soak), and moisturizing bath oils or humectants. Aqueous rinses generally also can be applied as sprays, although efficacy is greater as a total body rinse (Kwochka, 1995a).

Topical shampoo therapy is an important component of treatment or prevention of superficial and deep pyodermas. Antibacterial shampoos containing benzoyl peroxide, chlorhexidine, or lauricidin are indicated as adjuvant therapy for pruritus associated with pyoderma (see Chapter 10). Those most effective contain benzoyl peroxide or chlorhexidine (Kwochka, 1995b). Follow-up with a chlorhexidine rinse

ability. Hydroxyzine and amitriptyline tend to cause adverse reactions in cats. Clemastine (0.34 to 0.68 mg every 12 hours orally) may be effective.

A combination of both H_1 and H_2 receptor antagonists has been recommended but has not proved useful in animals thus far (Miller, 1993).

Fatty Acid Supplements

Studies that focus on the effects of dietary supplementation of EFA on canine atopy vary. Interpretation among clinical trials is complicated by the quantity and source of the PUFAs (GLA, EPA, and DHA), the lack of tissue fatty acid analysis, the duration of therapy (which often probably was not sufficiently long), and differences in outcome measures and adjuvant therapy. In addition, many of the studies were not controlled or blinded.

White (1995) provides a summary of the results of selected clinical trials implemented by various dermatologists. A study evaluating linoleic acid, linolenic acid, and EPA in dogs with atopy, flea allergy, and idiopathic pruritus (nonseasonal) found the response rate to the PUFA to be low (20% or less being controlled well; another 36% responded by a 50% reduction in pruritus). An open comparison of evening primrose oil, marine fish oil, and EFA products administered for 2 weeks found response in 25% of animals, but no product appeared more effective than the others. Responders worsened when supplementation was removed. Comparison of evening primrose oil alone or combined with marine fish oil found significant improvement with the sole product and increased (but not significant) efficacy with the combined product. A double-blind placebo-controlled crossover study with olive oil (placebo) or evening primrose administered for 9 weeks found clinical improvement with evening primrose oil. Two recent blinded studies have reported the benefits of EFA (EPA 180 mg and docohexaenoic acid 120 mg per 4.55 mg/kg) supplementation when administered for 6 weeks. Eleven of 16 dogs responded to fish oil, 3 of 16 responded better to corn oil, and 2 of 16 dogs responded to neither oil. A parallel study of 28 dogs supplemented with high doses of GLA (350 mg), EPA (250 mg), or linolenic acid (250 mg) and EPA (50 mg) found a benefit with all three supplements, suggesting that higher doses may be important to efficacy.

Cats seem to respond better than dogs, with up to 40% efficacy reported by some authors (Miller, 1993). Again, however, results of clinical trials tend to be conflicting. Pruritic cats with miliary dermatitis and other nonlesional causes of pruritis responded to 2 and 6 weeks of therapy of a linolenic acid/EPA supplement. In contrast, 12 weeks of therapy with evening primrose oil (3.7 mg linolenic acid/kg) or olive oil did not improve feline skin disease in another study. A 6-week course of evening primrose alone or when combined with marine fish oil resulted in improvement in feline pruritus and dermatitis; in contrast, marine fish oil by itself caused worsening of the skin disease. A 12-week course of therapy with evening primrose and sunflower oil also improved the skin and coat of cats with miliary dermatitis (White, 1995). White (1995) suggests that atopy should be most responsive to EFAs that are low in linoleic acid and high in linolenic acid and/or EPA/docohexaenoic acid. Addition of vitamins to the EFA supplement may facilitate efficacy of the EFA product. The appropriate ratio (n-6:n-3) is not clear, nor is the duration of therapy. A ratio of 5 to 10:1 has been suggested based on a study that found a decrease in LTB_4 and an increase in LTB_5 in the skin of dogs supplemented with diets containing these ratios (White, 1995). Response has been reported in as few as 7 to 14 days or as many as 9 to 12 weeks.

The most appropriate use of EFA for control of pruritus may be in combination with antihistamines or glucocorticoids (White, 1995). Success with fatty acid supplements also is most likely if an alternative product is tried if and when the first fails; adequate time is allowed to elapse before clinical assessment is complete; the goal is reduction rather than eradication of pruritus; or the goal is reduction of the dose of other drugs associated with adverse effects (e.g., glucocorticoids).

Behavior-Modifying Drugs

The use of behavior-modifying drugs is increasingly becoming in vogue; the proper use and side effects associated with these drugs are discussed in Chapter 25. Among the behavior-modifying drugs, those that are characterized by antihistaminergic effects might be preferred (e.g., doxepin or amitryptyline).

Behavior-modifying drugs have been used to treat feline pruritus, particularly that associated with psychogenic alopecia (Messinger, 1995). Psychogenic alopecia also has responded to naloxone (1 mg/kg subcutaneously, one dose), although time to recurrence of the abnormal behavior ranged from as short as 1 week to as long as 6 months (Messinger, 1995). The dopamine antagonist haloperidol (2 mg/kg intravenously) did not appear very useful long term when compared with a control for treatment of psychogenic alopecia (Messinger, 1995). Cats did, however, respond within 48 hours. Buspirone does not appear to be effective for control of psychogenic alopecia (Messinger, 1995). Fluoxetine has been useful for chronic licking in cats.

Combination Therapy

Combinations of drugs that alter the sensation or response to the sensation through different mechanisms of action should be considered. The combinations that appear to be most effective include fatty acid supplements (Dermcaps) with glucocorticoids (leading to a 25% to 50% reduction in the glucocorticoid dose) (Miller, 1993); antihistamines (trimeprazine) and glucocorticoids (an increase from 50% improvement with glucocorticoids alone to 76% improvement with the combination, with a 50% to 75% reduction in the glucocorticoid dose) (Scott, 1991); and fatty acid supplements with antihistamines (chlorpheniramine and Dermcaps in combination caused a 35% response in animals that responded to neither drug alone) (Miller, 1993). Combination of misoprostol with antihistamines is being investigated. Assessment at weekly intervals should be accompanied by a change in therapy if response has not been sufficient.

Generalized Demodicosis

Therapy for generalized demodicosis should be accompanied by proper nutrition, minimization of stress, and control of accompanying pyoderma. Self-cure can be expected in 50% of dogs less than 12 months of age, although no factors appear to be predictive of self-cure (Miller, 1995). The most efficacious treatment appears to vary in the literature. No single drug will cure all cases; up to 10% cannot be cured (Miller, 1995). Amitraz (19.9%) is the only Food and Drug Administration approved drug for treatment of demodicosis, although an Environmental Protection Agency registered solution is available. Amitraz is labeled for treatment at 2-week intervals (diluted to 250 ppm or 10.6 mL in 7.6 L). Original reports regarding its efficacy using the approved protocol apparently were inappropriately optimistic (90% predicted cure rates). Long-term cure rates according to the approved treatment regimen range from as little as 0% to 50% (0.025% or 250 ppm dip) (Scott, 1995b). Follow-up studies at greater concentrations have more favorable results.

Alternative concentrations include 500, 750, and 1000 ppm. Weekly dips of 250 to 500 ppm are curative in 75% to 80% of cases, respectively (Scott, 1995b). Long hair coats should be clipped and animals bathed first. Treatment should continue until two dips have occurred after negative scrapings, regardless of how many dips must occur. Weekly application may be implemented if biweekly therapy is not successful. Daily administration of a 0.125% solution (1000 to 1250 ppm using the large animal amitraz solution) on half of the body, alternating the other half of the body the next day should prove efficacious in 80% of nonresponders; feet should be soaked in the solution (Scott, 1995b). Oral vitamin E therapy at 200 IU/dog five times daily may enhance efficacy of amitraz, although this has not been proved (Scott, 1995b). Immunomodulators appear to be ineffective (Scott, 1995b).

Should amitraz fail, a macrolide antibiotic should be considered. Milbemycin at 1 and 2 mg/kg daily appears to cure 50% to 90% of dogs, respectively. Duration of therapy in one study ranged from 90 to 300 days; treatment should occur for 60 days past multiple negative skin scrapings. Side effects should be limited as long as 2.5 mg/kg is not exceeded (Miller, 1995). Ivermectin at 0.3 to 0.6 mg/kg per day orally (but not 0.2 to 0.4 mg/kg per week subcutaneously) also may be efficacious, with treatments being necessary for as long as 210 days. Because the drug is very bitter, administration in vanilla ice cream or apple sauce is recommended (Scott, 1995b). This dosing regimen is not safe for collies and related breeds. Testing for reaction to ivermectin involves administration of 0.125 mg/kg per day for 7 days. Alternatively, hospitalization might occur for the initial period during which a starting dose of 0.1 mg/kg is gradually increased to the maintenance dose.

Should relapse occur within 3 months, inadequate treatment is the most likely cause (Miller, 1995), and the therapeutic protocol can be repeated but for a longer duration. Later relapses probably reflect recurrence; repetition of the initial treatment protocol is not likely to be effective (Miller, 1995), and an alternative protocol should be selected.

Dermatophytosis

Treatment of dermatophytes is also addressed in Chapter 11. Establishment of the efficacy of selected treatment regimens is handicapped by the often self-resolving nature of the infection. Moriello (1995) emphasizes that, as with pyoderma, topical therapy alone is not sufficient for effective treatment of dermatophytosis. Indeed, several disadvantages are associated with topical therapy. Hairs protect spores; in addition, many commonly used topical antifungal solutions and shampoos are not sporicidal. Among those that are more efficacious are lime sulfur (1:16) and enilconazole (bottle dilution, but not licensed for use in the United States) (Moriello, 1995). Unfortunately, both of these topical products are associated with side effects: Enilconazole has caused death in some cats, and lime sulfer can be very irritating. Grooming after topical treatment increases the risk of toxicity. Pet owners are exposed to topical agents, increasing their risk. Occasionally, topical agents worsen infection, perhaps because of damage to the skin (mechanical scrubbing) during shampooing. The efficacy of topical ointments, creams, and gels is questionable. Among the topical ointments and creams, bifonazole is more effective than miconazole, but its efficacy also is questionable, particularly if infection involves haired skin. In addition, topical agents tend to be messy, are groomed by the animal, and encourage "spot" therapy. Nonetheless, topical therapy is an important adjuvant for treatment of dermatophytosis. Topical therapy will limit environmental contamination and contagion if spores on the hair coat are killed. The preferred topical product (Moriello, 1995) is lime sulfur (4 to 8 oz/gallon); higher concentrations are potentially irritating and cause exfoliation. Gauze sponges should be used to pat, not rub, the dip onto the skin. An Elizabethan collar should reduce the risk of ingestion.

Four drugs are used to systemically treat dermatophytosis: griseofulvin, ketoconazole, itraconazole, and fluconazole (see Chapter 11). Even in infections that will be self-resolving (self-cure generally occurs in 60 to 100 days), systemic antifungal therapy will hasten the time to recovery and thus is beneficial. Griseofulvin remains the drug of choice. Either the microsize dose (25 to 50 mg/kg divided or once every 24 hours) or the ultramicrosize dose (5 to 10 mg/kg orally once daily) can be administered. Because many animals are intolerant to ketoconazole, itraconazole is the second drug of choice should an animal fail or not tolerate griseofulvin therapy. Although improvement should be evident within 2 to 3 weeks of therapy, several weeks (generally 30 to 70 days) must lapse before a cure is effected. A comparison study in kittens infected with *Microsporum canis* found that time to resolution with griseofulvin (50 mg/kg orally divided or once every 24 hours) was 70 days versus 56 days with itraconazole (10 mg/kg orally once daily); the control group remained positive at 100 days. Therapy should be monitored by fungal cultures weekly or biweekly after 4 to 6 weeks of therapy and treatment continued until 2 to 3 consecutive weekly cultures are negative. Note that false-positive fungal cultures can occur after clinical recovery because of environmental contamination. Cats with questionable positive results should be isolated from the environment for 3 to 5 days and subsequently recultured. Terbenafine, a systemic antifungal approved for use in humans for treatment of dermatophytosis, has not been studied for efficacy or safety in animals. An unpublished pharmacokinetic study with cats (in Europe), however, indicates that a dose of 10 mg/kg once daily is appropriate; 10 to 30 mg/kg orally once daily has been suggested through Internet resources.

Cleansing of the environment is obviously critical in a cattery or kennel situation but can also be important in a single-animal household. Undiluted bleach and 1% formalin are the most effective products for resolving environmental contamination (Moriello, 1995). One hundred percent of spores are likely to be killed with this regimen; residual activity is likely to be greatest with undiluted bleach, followed by 1% formalin, enilconazole, and common household bleach diluted 1:10. Common household bleach is not as efficacious in killing spores as the other two products, but it is the least expensive and most readily available. Aqueous chlorhexidine is ineffective.

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Rational Use of Reproductive Hormones

34

Janice L. Cain

INTRODUCTION
PHYSIOLOGIC PRINCIPLES OF REPRODUCTIVE HORMONES
Hypothalamic Hormones
  Gonadotropin-Releasing Hormone and Its Analogues
  Oxytocin
Gonadotropins
  Luteinizing Hormone and Follicle-Stimulating Hormone
  Prolactin
Gonadal Steroids
  Estrogen
  Progesterone
  Testosterone
  Inhibitors of Gonadal Steroids
Prostaglandin $F_{2\alpha}$
COMMERCIAL AVAILABILITY OF REPRODUCTIVE HORMONES
Gonadotropin-Releasing Hormone and Its Analogues
Gonadotropins
Dopamine Agonists
Gonadal Steroids
Inhibitors of Gonadal Steroids
Miscellaneous
INDICATIONS FOR THE RATIONAL USE OF REPRODUCTIVE HORMONES
Estrus Induction
  Induction of Estrus in the Bitch
  Induction of Estrus in the Queen
Induction of Ovulation
  Ovulatory Failure in the Bitch
  Ovulatory Failure in the Queen
  Treatment of Follicular Ovarian Cysts in Bitches
  Treatment of Vaginal Hyperplasia/Prolapse
Luteal Insufficiency
Prevention or Termination of Estrus
Prolongation of Interestrous Intervals in the Bitch
Signs of Pseudocyesis
Pyometra and Postpartum Metritis
Pregnancy Termination
  Early Diestrus Protocol
  Midgestation Abortion
  Use of Dopamine Agonists
Medical Management of Dystocia
Adjunct Therapy for Mammary Gland Carcinoma
Urinary Incontinence in Spayed or Neutered Dogs
Cryptorchidism
Benign Prostatic Hyperplasia
Hypogonadism
MISUSES OF REPRODUCTIVE HORMONES
Treatment of Idiopathic Infertility
  Infertility in the Bitch
  Infertility in the Stud Dog
Treatment of Mismating/Pregnancy Termination
Treatment of Benign Prostatic Hyperplasia

INTRODUCTION

The use of reproductive hormones as pharmaceuticals should be based on knowledge of both the reproductive physiology in the species to be treated and the pathophysiology of the disorder at hand. Too often, hormonal therapies are used on the basis of knowledge of their function in other species or when the underlying disease process has not been fully studied. Although there are some specific indications for the rational use of reproductive hormones, they are commonly used inappropriately. This chapter includes a review of the basic physiology of the different hormones used in canine and feline reproduction, a discussion of their clinical availability, potential applications for their use, and common misuses of the products.

PHYSIOLOGIC PRINCIPLES OF REPRODUCTIVE HORMONES

Hypothalamic Hormones

Gonadotropin-Releasing Hormone and Its Analogues

Gonadotropin-releasing hormone (GnRH) is a hypothalamic decapeptide with the same amino acid sequence in all mammals. After pulsatile release from the hypothalamus, GnRH traverses the hypothalamic-hypophyseal portal system and activates anterior pituitary gonadotroph receptors. The pituitary responds by releasing luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in a pulsatile pattern (Concannon, 1993). Stimulation of the pituitary by GnRH must be in pulsatile form for repeated release of LH and FSH; after receptor activation, GnRH is rapidly deactivated and cleared. The frequency and amplitude of GnRH pulses vary depending on phase of the reproductive cycle. The frequency of GnRH pulsatile release in primates during folliculogenesis is every 70 to 90 minutes (Hull and Kenigsberg, 1987). It is this natural *pulsatile* secretion of GnRH and its short biologic half life that provide difficulty when attempting to use GnRH as a pharmaceutical. Investigations with specialized infusion devices for pulsatile delivery have successfully augmented fertility in a variety of species (Leyendecker et al., 1980; Johnson 1986; Cain et al., 1988), but the clinical application of such a method lacks practicality for routine use in small animal patients.

Gonadotropin-releasing hormone analogues are synthetically prepared substances that differ from GnRH by various amino acid substitutions in the peptide sequence. Analogues with a few amino acid substitutions can act as GnRH agonists because of their increased binding affinity and decreased clearance compared with GnRH. Heavily substituted analogues can cause receptor blockade and have an antagonist function. The result is a suppressive effect on the pituitary-gonadal axis. This axis is easily downregulated such that frequent or high dosing of a GnRH agonist will suppress the release of LH and FSH also (McRae et al., 1985).

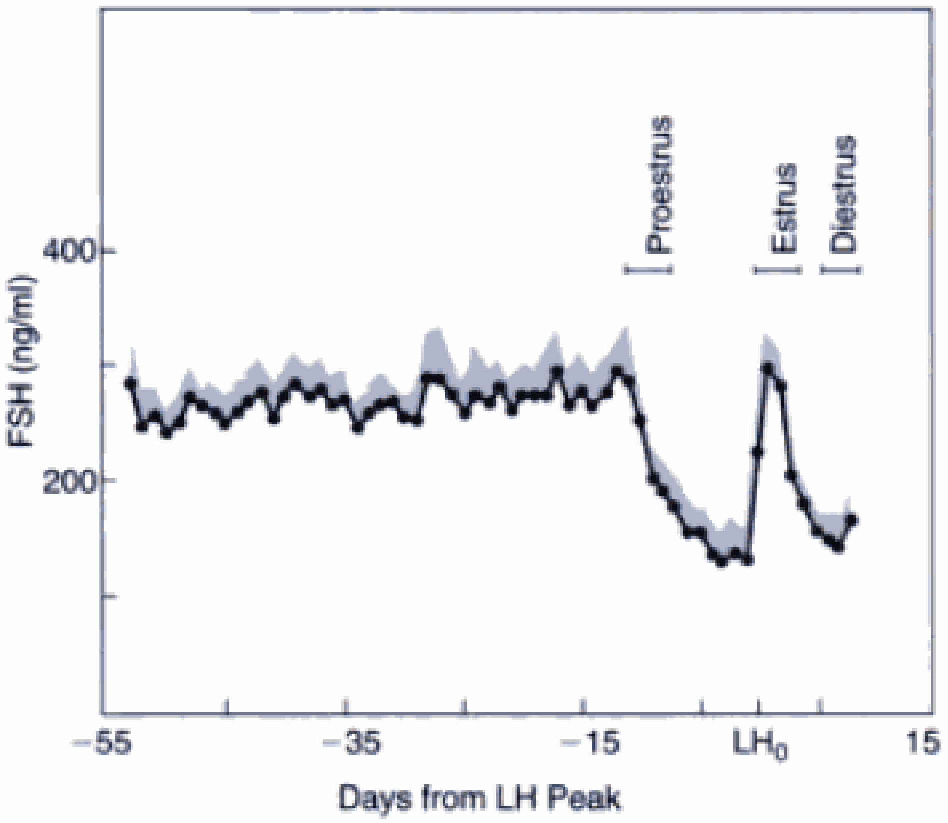

Figure 34–2. Concentrations of follicle-stimulating hormone (FSH) in canine serum throughout late anestrus, proestrus, estrus, and early diestrus. Stippled area is the standard error of the mean (bars indicate ranges of proestrus, estrus, and diestrus). (Reprinted with permission from Olson PN, Bowen RA, Behrendt MD, et al: Concentrations of reproductive hormones in canine serum throughout late anestrus, proestrus, and estrus. Biol Reprod 1982; 27: 1196.)

ues between intact and castrated dogs is possible (Olson et al., 1992).

Some species also produce placental gonadotropins. A luteotrophic gonadotropin produced by the human placenta (human chorionic gonadotropin [HCG]) has a potent LH-like effect in many species. A gonadotropin produced by fetal trophoblastic cells in horses is referred to as equine chorionic gonadotropin (eCG) or pregnant mare serum gonadotropin. In most species, eCG has a combination of FSH and LH activity. Additionally, eCG products commonly contain components of equine serum that can be antigenic when used as a pharmaceutical.

Prolactin

A relatively large polypeptide produced by the anterior pituitary, prolactin is luteotrophic in the bitch and queen (Onclin et al., 1993; Verstegen et al., 1993a). It is suspected that prolactin is also involved in the maintenance of the anestrus phase in the bitch (Concannon, 1993). Prolactin is under negative control by dopamine such that the administration of a dopamine agonist will inhibit prolactin secretion. Inhibition of prolactin secretion can be luteolytic during the second half of diestrus or pregnancy in the bitch (Onclin et al., 1993) and queen (Verstegen et al., 1993a). Various dopamine agonists have been investigated for inducing abortion and shortening anestrus (i.e., estrus induction). Bromocriptine is a dopaminergic drug that has been used in various protocols. Its use has not gained acceptance, however, because it commonly causes vomiting. The highly potent dopamine agonists cabergoline and metergoline have fewer or no apparent side effects, respectively. Metergoline's effect to decrease prolactin secretion may primarily result from blockade of central serotonin receptors and may function as a dopamine agonist only at higher doses (Krulich et al., 1981).

Gonadal Steroids

Estrogen

Produced by the ovary during folliculogenesis, estrogens affect target tissues causing vulvar edema, vaginal hyperplasia, sanguineous vulvar discharge in the bitch, and sexual attraction in both the bitch and queen. The bitch uniquely exhibits sexual receptivity when estrogen production decreases; serum concentration of estrogen peaks 1 to 2 days before the end of proestrus. Estrogen acts synergistically with progesterone to stimulate growth of endometrial and mammary glands, and estrogen priming may be important before the natural effect of oxytocin on the myometrium during parturition (Carruthers, 1986). Male production of estrogen is primarily from the Sertoli cells, although conversion from pregnenolone produced by the interstitial cells is possible. Excessive production of estrogens by Sertoli cell tumors and, less commonly, by other testicular tumors results in male feminizing syndrome. Estrogens are involved in receptor sensitivity and feedback influence on the hypothalamic-pituitary-gonadal axis.

The adverse effects of estrogen (i.e., bone marrow aplasia, pyometra, infertility) have been documented in dogs after administration of any estrogen preparation (Teske, 1986; Bowen et al., 1985). The unique sensitivity of dogs to estrogen toxicity may be due to the relatively weak binding affinity of sex-steroid binding proteins for estrogen in the dog. The result is a decrease in the inherent buffering mechanism that would otherwise regulate the amount of free hormone available to penetrate cell membranes. Estrogen toxicity can occur with exogenous or endogenous estrogens (e.g., Sertoli cell tumors, ovarian follicular cysts, and ovarian neoplasia).

Progesterone

As the main progestational hormone in both bitches and queens, progesterone is produced by corpora lutea after ovulation. The bitch continues to produce progesterone during diestrus; serum concentrations of progesterone are indistinguishable in concentration or duration of production from that of pregnancy. The decline of progesterone and increase in prolactin production at the termination of diestrus cause the clinical manifestations of pseudopregnancy in the nonpregnant bitch. This is a demonstration of a normal physiologic occurrence that should not be confused with a pathologic state. There is some variation between bitches regarding the maximum amount of progesterone produced in midgestation (or mid-diestrus), with levels reaching 80 to 100 ng/mL in some individuals. The minimum serum progesterone concentration necessary to maintain pregnancy appears to be 2 ng/mL (Root and Johnston, 1995). The minimum amount of progesterone required to sustain pregnancy in the queen has not been determined; however, serum progesterone concentrations of less than 1 ng/mL for several days occurred before termination of pregnancy was observed in one study (Verstegen et al., 1993a).

Placental production of progesterone by the queen during the latter half of pregnancy had been suggested as a requirement to maintain pregnancy. It has been suggested, however, that corpora lutea of the queen are necessary for progesterone production throughout pregnancy (Verstegen et al., 1993b). During pseudopregnancy in queens (i.e., nonfertile ovulation), peak luteal activity appears to occur at days 10 to 15 and then declines to basal values by days 35 to 40 (Shille and Stabenfeldt, 1979).

Unique to the bitch, progesterone is produced before ovulation by follicular luteinization, approximately concurrent with the preovulatory LH peak. Serial evaluations of serum progesterone concentrations during proestrus/estrus can be used to indirectly determine the preovulatory LH peak and thus determine the time of ovulation in the bitch. This methodology, known as *ovulation timing*, is used to improve breeding management. The bitch typically exhibits sexual receptivity (behavioral estrus) when the serum concentration of estrogen is decreasing and progesterone is increasing.

Synthetic progestational compounds (progestagens) are commercially available. Megestrol acetate has been marketed as a drug to suppress estrus or inhibit ovulation, depending on the time and dose of administration. The method by which progestagens inhibit folliculogenesis and ovulation is not precisely understood. It appears that while megestrol acetate will not decrease the serum concentration of LH that is already at low basal levels, it can possibly prevent the increases in LH that normally occur at the end of anestrus (Concannon, 1993).

Testosterone

Produced by the interstitial cells of the testes, testosterone is necessary for gonadal development, spermatogenesis, and libido in the male. The normal function of Sertoli cells to promote spermatogenesis depends on an intratesticular testosterone concentration that greatly exceeds circulatory levels (Carruthers, 1986). Pharmacologic administration of androgens, including testosterone, can induce infertility by negative inhibition of LH and FSH release, which are necessary for spermatogenesis. Testosterone is converted within the prostate to dihydrotestosterone, which promotes development of this gland and the eventual formation of benign prostatic hyperplasia in mature dogs.

Testosterone and the androgenic steroid mibolerone have been used to suppress ovarian activity and thereby prevent estrus cycles in the bitch. Mibolerone is specifically approved for this use, although the duration of time from discontinuing administration to the occurrence of the next estrous cycle is variable. Persistent anestrus (i.e., lack of return to estrous cycles) has been a problem in some greyhound bitches treated with testosterone to prevent estrus cycles during racing.

Inhibitors of Gonadal Steroids

Tamoxifen is an estrogen antagonist that has been used to treat women with mammary carcinoma. Tamoxifen appears to have, at least in part, a direct estrogenic effect in the bitch. Some bitches treated with tamoxifen had observable vulvar edema, sanguineous vaginal discharge, and, in some cases, pyometra of the uterine stump (Kitchell and Fidel, 1992). Tamoxifen and clomiphene, another antiestrogenic compound, have been used to promote superovulation in women, possibly by promoting an increase in endogenous FSH release.

Antigestagens are agents that inhibit the effect of progesterone and have been investigated as abortion agents in humans (i.e., mifepristone, RU 486). Preliminary studies have documented the effectiveness of mifepristone to terminate pregnancy in bitches (Concannon et al., 1990).

Finasteride is another useful inhibitor of gonadal steroids. Testosterone is converted to dihydrotestosterone (DHT) within the prostate by the action of the enzyme 5α-reductase. Trophic in its effect, DHT induces benign prostatic hyperplasia. Finasteride inhibits the action of 5α-reductase, thereby reducing DHT concentrations within the prostate. Developed for use in men with prostatic hyperplasia, finasteride has been investigated for similar use in dogs (Cohen et al., 1991).

Prostaglandin $F_{2\alpha}$

Administration of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) induces a direct luteolytic effect in bitches and queens during pregnancy or diestrus. Induction of luteolysis depends on dose, frequency of drug administration, and time during diestrus that the drug is administered. After day 30 of diestrus, $PGF_{2\alpha}$ is reliably luteolytic in both the bitch (Feldman et al., 1993) and queen (Shille and Stabenfeldt, 1979). Corpora lutea are relatively resistant to luteolysis by $PGF_{2\alpha}$ during the first 5 days of diestrus in the bitch (Romagnoli et al., 1993). There is evidence that $PGF_{2\alpha}$ will cause either a transient decrease in progesterone production or complete luteolysis when administered during early diestrus after day 6 (Romagnoli et al., 1993). In addition to a direct luteolytic effect, $PGF_{2\alpha}$ also has a stimulatory action on the myometrium to evacuate uterine luminal contents. The drug is therefore effective as an abortifacient and for the treatment of pyometra in the bitch and queen.

Additional effects of $PGF_{2\alpha}$ administration include panting, nausea, vomiting, diarrhea, hypersalivation, and tachycardia in dogs and vocalization, mydriasis, and possibly vomition and diarrhea in cats. These adverse clinical signs usually stop within 20 to 30 minutes of drug administration. The drug is preferably administered after fasting in the dog and cat to decrease the incidence of vomiting. The adverse effects of $PGF_{2\alpha}$ are potentially dose related, although there is individual sensitivity, and signs may abate after repeated dosing. Although extremely rare, cardiovascular collapse after $PGF_{2\alpha}$ administration is possible.

Most protocols using $PGF_{2\alpha}$ are based on the formulation of dinoprost tromethamine. This product is not approved for use in dogs or cats in the United States. Although the use of this product in the bitch and queen is considered experimental and informed owner consent is advised, the use of $PGF_{2\alpha}$ is established in the veterinary literature. The more potent synthetic $PGF_{2\alpha}$ analogues (cloprostenol and fluprostenol) are not recommended for the dog and cat; studies regarding the use of these compounds are investigational at this time.

Table 34–1. Uses of Reproductive Hormones for Dogs and Cats

Indication	Hormone Used	Considerations
Estrus induction	All classes of reproductive hormones	No protocol proven effective and safe with readily available products at this time
Induction of ovulation		
Ovulatory failure	hCG or GnRH to induce ovulation	Cannot determine follicular maturity to administer at correct time
Ovarian cysts	hCG or GnRH to induce luteinization	Often ineffective, may require surgical treatment, need to differentiate neoplasia
Vaginal hyperplasia	hCG or GnRH to hasten ovulation	Not proved to shorten time for spontaneous recovery
Luteal insufficiency	Progesterone to maintain gestation	Potentially teratogenic, luteal insufficiency is rare; need diagnosis before treatment attempted
Estrus prevention	Mibolerone or megestrol acetate	Mibolerone: unpredictable return to estrus after withdrawal; megestrol acetate: potential for infertility, pyometra
Signs of pseudocyesis	Mibolerone	None
Pyometra/postpartum metritis	$PGF_{2\alpha}$	Transient side effects of $PGF_{2\alpha}$, need careful evaluation and supportive clinical care
Pregnancy termination	$PGF_{2\alpha}$, dopamine agonists	Transient side effects of $PGF_{2\alpha}$; unavailability of some dopamine agonists
Dystocia	Oxytocin	Overdosage can induce uterine tetany and fetal demise
Mammary gland carcinoma	Tamoxifen	Controversy as to efficacy
Urinary incontinence	DES or testosterone	Phenylpropanolamine effective with fewer side effects
Cryptorchidism	hCG or GnRH	Ethical question
Benign prostatic hyperplasia	Finasteride	Only preliminary information available, costly
Hypogonadism	Gonadotropins	Rare condition, difficult to document

Abbreviations: DES = diethylstilbestrol; GnRH = gonadotropin-releasing hormone; hCG = human chorionic gonadotropin; $PGF_{2\alpha}$ = prostaglandin $F_{2\alpha}$.

Table 34–2. Hormones Used to Induce Estrus in Bitches

Hormone Classification	Considerations	Drawbacks
GnRH	Leaves normal feedback mechanisms intact; drug is available, not expensive	Requires expensive, cumbersome pump for drug delivery
GnRH analogues	Success in preliminary reports; subcutaneous administration or delivery by implanted infusion devices	Not commercially available
Gonadotropins	Many different protocols proposed	Most successful protocol used P.L.H., which is no longer commercially available. Hormones that are available (eCG, hCG, FSH) are unsuccessful Can cause hyperstimulation and hyperestrogenism
Estrogen	Oral administration of DES, a readily available compound	Potentially toxic compound; need to evaluate future fertility and optimal dosing schedules before offering to client-owned animals. Information available based on one study at this time
Dopamine agonists	Shortened interestrous interval by decreasing prolactin production	Cost of the newer dopamine agonist cabergoline, which has decreased adverse effects; bromocriptine available but associated with protracted vomiting. Relatively long duration of treatment needed (i.e., 40 days) to induce estrus. Preliminary reports of their use; additional investigation is needed

Abbreviations: DES = diethylstilbestrol; P.L.H. = luteinizing hormone; eCG = equine chorionic gonadotropin (also known as pregnant mare's serum gonadotropin [PMSG]); FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; hCG = human chorionic gonadotropin.

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Figure 34–3. A laboratory beagle fitted with a harness and the Pulsamat infusion pump. The pump reservoir is connected to a jugular catheter via specialized tubing. (Reprinted with from Cain JL: The use of reproductive hormones in canine reproduction. Probl Vet Med 1992; 4: 456.)

mercially available, have been investigated as agents to induce estrus in bitches. The advantage of GnRH analogues is their relatively longer bioavailability and increased potency. Concannon (1989) reported the use of [D-Trp^{6}Nme-Leu^{7}Pro^{9}NEt]GnRH administered via a constant infusion device. Twenty-four bitches received 1.7 to 2.5 μg/kg/day subcutaneously (SC) for 14 days; nine bitches ovulated and whelped litters. In a preliminary report, the use of [D-Trp^{6}Pro^{9}NEt]GnRH was administered to bitches (1 μg/kg SC every 8 hours) by the following protocol: every 8 hours SC injections until the observation of behavioral estrus after which treatment was continued for another 3 days at half the original dose (i.e., 0.5 μg/kg SC every 8 hours) (Cain et al., 1990). Four of six bitches treated with this protocol whelped litters as a result of an induced estrus.

The gonadotropins FSH and LH have been investigated with numerous protocols as agents to induce estrus in the bitch. Most protocols use either eCG or FSH to stimulate folliculogenesis and hCG to induce ovulation. Some protocols additionally utilize DES administered before gonadotropins; estrogen can increase the responsiveness to gonadotropins. Gonadotropin protocols are largely unreliable and can induce adverse effects (i.e., ovarian hyperstimulation with hyperestrogenism), and with some protocols an abnormal luteal phase was detected (Cain, 1989). One report indicated great success with the currently unavailable product P.L.H. (Burns-Biotech) (Moses and Shille, 1988), although it is unknown what the relative biopotency of FSH and LH was in the product marketed as P.L.H. That protocol was investigated using greyhound bitches that had previously received testosterone to suppress estrus during racing. Those bitches had not received testosterone during the 12 months before inclusion in the study, and none of the bitches had an observed proestrus or estrus during that period of time.

The protocol was as follows: DES was administered (5 mg/bitch per day orally [PO]) until proestrus was evident and then for 2 days thereafter. If no signs of proestrus were observed by day 7 of DES treatment, the dose was doubled (10 mg/bitch per day PO) until a response was elicited (not to exceed 7 additional days of DES therapy). On day 5 of proestrus, P.L.H. was administered (5 mg/bitch intramuscularly [IM]), and on days 9 and 11 of proestrus FSH was administered (10 mg/bitch IM) (Moses and Shille, 1988). All seven bitches in this report became pregnant when bred during an induced estrus. This method utilized gonadotropin administration in a reverse sequence to that of other reported studies. Because the LH used in this study was no longer available, an attempt to modify the protocol using hCG in place of LH was attempted, but results were disappointing (Shille et al., 1989).

Subsequent studies into the use of DES as a sole agent to induce estrus may indicate that the DES used in other protocols was the primary active agent, and perhaps the administration of additional hormone products decreases the response. Fertile estrus has been induced in bitches by the sole administration of oral DES. In a preliminary report, DES (5 mg/bitch PO) was administered daily until proestrus was observed and then for 2 days thereafter (Bouchard et al., 1993). The DES therapy continued for 6 to 9 days and resulted in an induced proestrus lasting 0 to 2 days (range) and an estrus duration of 15 to 26 days (range). The preovulatory LH peak occurred 13.5 ± 3.7 days after the last day of DES treatment, although one treated bitch did not have a detectable preovulatory LH peak. All five treated bitches in this study became pregnant, four bitches whelped at term, and one bitch aborted. The lengths of proestrus and estrus and the sizes of the litters did not significantly differ between treated and control groups ($n = 5$ in each group). The bitches used in this study were treated during a defined period of anestrus (95 to 129 days; mean 107 ± 13 days), which resulted in a shorter period of anestrus than is normal for the colony (175 ± 87 days). Additional investigation into the use of DES as an agent to induce fertile estrus is needed before client-owned bitches are treated. *The optimum dosage schedule and potential for toxicity need to be assessed.*

Another method to shorten the naturally long interestrus interval in the bitch is by the administration of a dopamine agonist to decrease prolactin secretion. Prolactin secretion may alter ovarian responsiveness to gonadotropins; the continued presence of prolactin during anestrus may be responsible for the duration of this phase of the estrous cycle. Decrease in prolactin secretion can shorten the length of anestrus and can induce estrus if treatment occurs during late anestrus. Bromocriptine (20 μg/kg twice daily administered 112 ± 4 days after the last onset of proestrus) was used in one study to decrease the interestrus interval in bitches (Van Haaften et al., 1988). Bromocriptine causes vomiting, and investigation into its use has been largely replaced by the dopaminergic drugs cabergoline and metergoline. Two protocols using metergoline were reported in one study (Handaja Dusma and Tainturier, 1993). Bitches were treated with metergoline (12.5 mg/bitch IM every 3 days) until the onset of proestrus. Response to therapy was considered positive if proestrus was observed within 40 days after the first day of treatment; 18 of 20 bitches so responded. Ten of these bitches received no additional treatment and were bred, and nine produced litters. Eight other bitches responding to metergoline were additionally treated with hCG (500 IU/bitch IM) during late proestrus. Six of these bitches ovulated, and four achieved pregnancy.

Overall, the metergoline protocol without hCG was more effective in producing pregnancy.

The administration of $PGF_{2\alpha}$ can also shorten the interestrous interval if administered during diestrus. Diestrus normally has a duration of 65 to 70 days in the bitch, and luteolytic therapy with $PGF_{2\alpha}$ abbreviates this phase of the estrous cycle. Bitches that have undergone luteolytic therapy will still enter a phase of anestrus for a variable period, but the return to proestrus/estrus can be sooner than expected by 1 to 2 months.

Induction of Estrus in the Queen

The domestic cat has been used as a model for reproductive techniques that can apply to preservation of the nondomestic large felines (Goodrowe et al., 1989). Queens are apparently sensitive to effects of gonadotrophins administered to induce folliculogenesis, but production of anovulatory follicles or cysts can result. The administration of eCG as a single bolus (100 IU) to anestrus queens, followed in 5 to 7 days by a single injection of hCG (50 IU), resulted in a pregnancy rate that was comparable with natural matings (Cline et al., 1980). Daily administration of F.S.H.-P (2 mg/queen per day IM) for 5 to 7 days results in 72% of queens that will mate and deliver normal offspring (Wildt et al., 1978).

Induction of Ovulation

Ovulatory Failure in the Bitch

Ovulation failure is rare in the bitch. Too often, bitches are suspected of ovulatory failure when they have seemingly long proestrous and estrous phases, produce small litters, or fail to conceive. Bitches can have signs of estrus, and a fully cornified vaginal smear, for up to 21 days before natural spontaneous ovulation. Also, bitches can have a split estrus: signs of proestrus/estrus without ovulation, a period of anestrus for several weeks, and then return to proestrus. Often the second estrus will be ovulatory and fertile. Split estrus is more common in pubertal bitches but can occur in mature bitches.

Ovulation cannot be reliably detected with ultrasonography, and direct visualization by laparoscopy is not possible due to the ovarian bursa (nor would it be practical); thus, the determination of ovulation can only be attempted indirectly. Serum progesterone concentration can be measured in bitches that historically fail to conceive. The timing of the progesterone measurement is important. It is recommended to evaluate progesterone during the first few weeks of diestrus. Serum concentration of progesterone should be in excess of 5 ng/mL (and generally in excess of 20 ng/mL) at this time. A progesterone level of less than 2 mg/mL indicates either ovulation failure or luteal insufficiency. Values between 2 and 5 ng/mL are also abnormal and can indicate ovulatory failure, luteal insufficiency, or an uncommonly low progesterone production during diestrus.

Bitches that have normal proestrus and estrus but apparently do not ovulate can be given hormonal products to induce ovulation. To mimic the preovulatory LH peak, either GnRH or hCG can be administered at the point of follicular maturation. The determination of follicular maturity is difficult. Incorrect administration (i.e., inappropriate timing) of either preparation can cause preovulatory luteinization of follicles without ovulation or the ovulation of immature, nonviable ova. It has been recommended to administer either GnRH (50 µg/bitch IM) or hCG (500 to 1000 IU/bitch IM) on either the day before or the day after the first breeding (Burke, 1986). Bitches can begin sexual receptivity several days before or after spontaneous ovulation; therefore, this protocol is questionable. It may be advisable to measure serum LH concentration daily during proestrus and estrus and administer either GnRH or hCG on the day of the natural preovulatory LH peak. This presumes that the bitch produces enough LH to measure a peak but either does not produce enough LH to cause ovulation or has another factor inhibiting ovulation. Bitches that fail to ovulate may not produce a measurable LH peak, in which case this recommendation would also fail. Clearly, more investigation is needed in this area.

Ovulatory Failure in the Queen

Queens can be sexually receptive before follicular maturation. Limited mating before the third to fourth day of estrus can result in an attenuated LH secretion and ovulatory failure (Banks and Stabenfeldt, 1982). Additionally, although an LH response after one mating will occur, a maximal LH response ensuring ovulation of all mature ova will more likely occur if numerous matings over a several-day period is allowed. In one report, 10 of 48 queens ovulated after a single mating, whereas 30 of 36 ovulated after multiple matings (Wildt et al., 1980). Optimal breeding management includes mating three times per day at 4-hour intervals throughout estrus.

If it is determined that a queen fails to ovulate despite appropriate management, induction of ovulation can be attempted. Protocols with either hCG or GnRH have been reported as follows: hCG 500 IU/queen IM on day 1 of estrus (Wildt and Seager, 1978); and GnRH 25 µg/queen IM on day 2 of estrus (Chakraborty et al., 1979).

Treatment of Follicular Ovarian Cysts in Bitches

Estrogen-producing follicular cysts can cause prolonged proestrus, nymphomania, estrogen toxicity, and infertility. A luteinized follicular cyst can produce estrogen or progesterone and may cause persistent anestrus and infertility. Ovarian cysts are often detected during ovariohysterectomy of older bitches as incidental findings. The detection of a cystic ovarian structure via ultrasonography can be a significant finding. The possibility of a cystic ovarian neoplasm, which can produce clinical signs identical to benign cysts, must be considered and is more likely in bitches over 5 years of age. The measurement of estrogen and progesterone concentrations from the fluid of percutaneously aspirated ovarian cysts can assist the diagnosis of a functional cyst; this will not, however, differentiate between a cyst and neoplasm.

Whether or not to attempt therapeutic intervention when an ovarian cyst is detected is controversial; ovarian cysts can spontaneously regress (Davidson and Feldman, 1995). Estrogen-producing follicular cysts can be luteinized with

tance of surgical castration in the dog make treatment with GnRH analogues for such cases unlikely. The advantage of medical treatment versus surgical castration is the potential reversibility of infertility with cessation of down-regulation therapy, although the androgen-dependent disorder would likely recur.

Successful treatment of benign prostatic hyperplasia using finasteride has been reported (Cohen et al., 1991). The advantage of finasteride administration is the maintenance of sperm production because finasteride decreases intraprostatic dihydrotestosterone concentrations and will not affect intratesticular testosterone concentrations. Recommendations have been to administer finasteride to dogs at the dosage currently used for men: 5 mg/dog PO once daily. Whether a lower or less frequent dosing regimen is possible remains to be investigated. The disadvantage of finasteride administration is that it is potentially teratogenic such that men receiving finasteride are advised not to father children. *Investigation into the appropriate withdrawal period before breeding needs to be conducted before finasteride can be routinely administered to breeding dogs.*

The use of progestagens (i.e., medroxyprogesterone and megestrol acetate) have also been reported as methods of treatment to decrease prostatic hypertrophy and maintain sperm production. The potential adverse systemic effects of these compounds (i.e., effects on growth hormone production, liver function, insulin secretion, mammary gland disease) make this method of treatment less appealing.

Hypogonadism

Hypogonadotropic hypogonadism, a congenital condition in which the pituitary fails to produce gonadotopins, occurs in men. Affected men can respond to gonadotropin replacement therapy with resultant fertility. Hypothalamic or hypogonadotropic hypogonadism has not been documented to occur in a congenital form in dogs. Acquired pituitary dysfunction can occur in dogs with space-occupying neoplasms, but the diagnosis of hypogonadism is difficult. Lack of negative feedback inhibition causes dogs with primary testicular degeneration/atrophy to have high serum LH and FSH concentrations. If primary pituitary failure was the cause of azoospermia, the serum FSH and LH concentrations would be low. At present, FSH assays are not clinically available for the dog. Because of the nature of LH secretion, challenge testing is recommended to evaluate pituitary function.

Treatment of this form of infertility depends on the etiology of the pituitary disease; fertility may be unimportant in view of the dog's general health. Although the prognosis for return to fertility is guarded, one protocol using gonadotropin replacement therapy is to administer 500 IU hCG biweekly (SC or IM) and FSH at either 1 mg/kg IM every 48 hours or 25 mg/dog SC once weekly (Feldman and Nelson, 1996). Because spermatogenesis and spermatozoa maturation requires approximately 77 days, therapy must be continued for 3 months before the effectiveness of this protocol can be evaluated.

MISUSES OF REPRODUCTIVE HORMONES

Some reproductive hormones have been misused for many years (Table 34–3). Assumptions made on incomplete information about canine reproductive physiology and lack of option alternatives led to the development of these protocols in the past. Current knowledge and other alternatives (i.e., for mismating in bitches) have resulted in the discontinuation of these practices, which are now considered inappropriate.

Treatment of Idiopathic Infertility

Infertility in the Bitch

Physiologic processes that control folliculogenesis in the bitch are complex and involve precise, minute amounts of hypothalamic and pituitary hormones that are sensitively controlled by the ovarian feedback loop. To interrupt the hypothalamic-pituitary-ovarian axis pharmacologically leads to dysfunction, rather than an augmentation, of the system. The rational administration of GnRH requires pulsatile administration, the use of GnRH analogues results in down-regulation, and the use of gonadotropins is largely unsuccessful to induce fertile estrus in *known* fertile bitches. There is no evidence to support the use of these hormones in bitches with a history of infertility or decreased fecundity. Careful evaluation of the underlying causes of infertility and optimal breeding management with

Table 34–3. Misuses of Reproductive Hormones

Disorder	Hormone Misused	Considerations	Alternatives
Female infertility	GnRH, gonadotropins	Alteration of feedback loop decreases fertility	Appropriate diagnostic evaluation; ovulation timing and optimal breeding management
Male infertility	GnRH, gonadotropins, testosterone	Lack of effect or decreased fertility; testosterone decreases spermatogenesis	Appropriate diagnostic evaluation
Mismating	Estrogens (DES or ECP)	Can cause bone marrow toxicity, infertility, pyometra	Early or late diestrus treatment with $PGF_{2\alpha}$
Benign prostatic hyperplasia	Estrogen (DES)	Can cause squamous metaplasia and increased risk of bacterial prostatitis	Castration; treat with finasteride

Abbreviations: DES = diethylstilbestrol; ECP = estradiol cypionate; GnRH = gonadotropin-releasing hormone; $PGF_{2\alpha}$ = prostaglandin $F_{2\alpha}$.

Table 2. Offices of the Center for Veterinary Medicine

- Department of Health and Human Services
  - Food and Drug Administration (888-463-6332)
    - Center of Veterinary Medicine (301-594-1755)
      - Office of the Center Director (301-594-1740)
        - Director: Stephen F. Sundlof, DVM, PhD
        - Deputy Director: Michael J. Blackwell, DVM, MPH
        - Associate Director for Policy and Regulations
      - Office of Management and Communications (301-594-1752)
        - Director: Robert W. Sauer
      - Office of New Animal Drug Evaluation (301-594-1620)
        - Director: Claire M. Ladhers, PhD, FCB
      - Division of Therapeutic Drugs for Non-food Animals
        - Melanie R. Berson (301-825-7543)
      - Companion and Wildlife Drugs
        - Team Leader: Elizabeth A. Luddy, PhD (301-827-0133)
      - Division of Therapeutics for Food Animals
        - Steve Vaughn (301-827-7580)
      - Office of Surveillance and Compliance (301-827-6644)
        - Director: Linda R. Tollefson, DVM, MPH
      - Office of Research (301-827-8010)
        - Director: Norris E. Alderson, PhD
      - Communications Staff
        - Director: John Scheid (301-827-6514)
        - Deputy Director: Linda Grassie (301-827-6513)
      - Freedom of Information Officer: Marilyn H. Broderick (301-827-6510)

tion have done an excellent job in putting together and publishing symposia that delineate and discuss the implications of FDA actions. In addition, the American College of Veterinary Clinical Pharmacologists and the American Academy of Veterinary Pharmacology and Therapeutics provide guidance through publications and consultation. Finally, the FDA appears to be willing to answer any questions or concerns one might have regarding the use of drugs in animals. In the Center for Veterinary Medicine, the Office of New Animal Drug Evaluation consists of the Division of Therapeutic Drugs for Non-food, which in turn contains a Companion and Wildlife Drugs. Note that there are other federal agencies that regulate the use of drugs in animals, including the Environmental Protection Agency, the Animal and Plant Health Inspection Service, and others (see Table 1).

Drugs Defined

A drug is well defined by the FDA. It must be recognized as such (e.g., by the U. S. Pharmacopeia; USP); intended for diagnosis, cure, mitigation, or prevention of disease in humans or other animals (note that the FDA defines humans as animals); intended to affect body structure or function; or a component of any of the above. In 1968, the FDA first made a distinction between human and veterinary-labeled drugs. As with most regulations since that time, the distinction reflected a concern for human food safety. At that time, an animal drug was adulterated if used in an extralabel fashion. Thus, a veterinarian could not modify a dosing regimen, therapeutic intent, and so forth of a drug without being liable in both criminal and civil courts. Currently, a *New Animal Drug* is "any drug intended for use in animals other than man . . . not recognized . . . as safe and effective under conditions on the label." A drug's label includes the label on the product as well as any accompanying material. A prescription drug is defined by whether or not adequate directions can be prepared for use of the drug by a layperson. Any drug for which this is possible must be sold as an *over the counter* (OTC) preparation; any other product is a prescription (Rx) product that must bear the phrase: "Caution: federal law restricts this drug to use by or on the order of a licensed veterinarian." Trying to identify the approval status of a drug can be difficult. Obviously, if the label has this cautionary statement, an NADA (new animal drug application) exists for the drug and it can be used legally *according to the label specifications*. Determining whether an NADA exists for a drug can, however, be difficult. If the drug is listed in the veterinary versions of the *Physician's Desk Reference* (i.e., the *Veterinary Drugs and Biological Products* published by Medical Economics or the *Compendium of Veterinary Products* published by Bayer Animal Health [both basically are copies of package inserts]), then the drug has an NADA. Note that drugs listed in veterinary textbooks (including formularies, pharmacology texts, internal medicine texts, and so forth) do not necessarily have an NADA. Other sources include members of the American College of Veterinary Clinical Pharmacology, the FDA Green Book, or the *Handbook of New Animal Drugs*, published by Shotwell and Carr.

The Drug Approval Process

From discovery of a new compound (including isolation and synthesis) through its development (including establishing safety and efficacy) to its marketing involves researchers and clinicians and a consortium of regulatory, industrial, and often academic investigators.

Human Drugs

The approval process for (human) drugs in the United States has been described as the most vigorous in the world, costing on average $359 million to move a drug from the laboratory to the patient. After identification and isolation of a compound, its safety is established in laboratory animals. *Preclinical testing* studies include acute and chronic toxicity studies focusing on the reproductive status, mutagenicity, and carcinogenicity of the drug. A safe dosing range is established, requiring both pharmacokinetic and pharmocodynamic (dose response) studies. At this point, if the compound is considered a potential candidate for approval, an *IND (Investigational New Drug)* is filed by the sponsor, along with protocols for clinical testing. This phase requires approximately 5 to 8 years, and generally only 1 drug in 5000 evaluated succeeds in this phase. At this point, if the compound is considered a potential candidate for approval, an IND is filed by the sponsor along with protocols for clinical testing. Approximately 2000 INDs are filed with the FDA each year. Long-term safety studies will continue in animals as the drug enters Phase I clinical trials in humans.

The *clinical phase* of drug approval involves three distinct phases of clinical trials that provide the basis of the drug label. *Phase I* is conducted on a small number of

animals (i.e., a drug approved in Canada, Mexico, or Europe but not the United States). Occasionally, the FDA may recommend that an INAD be obtained for the use of a drug recently approved for use in humans because data regarding the safety of the drug are probably still being collected for humans. An INAD may also be recommended if the drug is toxic (especially carcinogenic) or it is scheduled (regulated by the Drug Enforcement Agency). If an INAD is obtained, veterinarians must keep records regarding the use of the drug and must notify the FDA everytime a shipment is requested or an adverse reaction occurs.

Extrapolation of human drugs to animals should be accompanied, whenever possible, by scientific studies that support proper dosing regimens. Recommendations regarding the extrapolation of dosing regimens among species is addressed in Chapter 2.

Generic Drugs

Pharmacists can dispense an equivalent, less expensive, nonproprietary (generic) drug without prescriber approval. An exception occurs if a state has a mandatory substitution law or if the brand name product is dispensed along with a Dispensed as Written (D. A. W.) order. Generics may be pharmaceutically equivalent but may not be therapeutically equivalent. Those tested by the FDA and found to be therapeutically equivalents are listed in *Approved Drug Products with Therapeutic Equivalence Evaluations*, otherwise known as "the Orange Book." Generic products not only contain the same active ingredient as the proprietary drug but also meet bioequivalence standards. Substitutions of generic drugs for proprietary drugs are recommended only for those drugs shown to be therapeutically equivalent. Examples of drugs that are not therapeutically equivalent to their brand name counterparts include digoxin, phenytoin, conjugated estrogens, and slow-release theophyllines. The Orange Book addresses therapeutic equivalence in human medicine, and veterinary clinicians should not mistake therapeutic equivalence established in humans to be the same in animals.

Schedule Drugs

Drugs considered to be associated with a potential for abuse or physical dependence are restricted by the FDA such that specific requirements must be met when the drugs are prescribed. The classification reflects the perceived level of potential abuse or physiologic or psychological dependence, with Schedule I being the most severe (Table 5). The specific requirements regarding the purchase, storage, prescription, and record keeping for controlled substances vary with each state. Schedule I drugs have the highest potential of abuse and physical dependence. These drugs have no acceptable medical use in the United States and are not to be prescribed, but they can be obtained for research purposes. Heroin is the most notable example.

Schedule II drugs, exemplified by cocaine and morphine, are considered to have a high potential for abuse and dependence but have some medicinal worth. Prescription refills are not allowed for these drugs, and they cannot be prescribed by telephone. Selected states require a special prescription blank. Schedule III drugs, exemplified by selected opioids and barbiturates, have a moderate potential for dependence and have an accepted therapeutic use. Schedule IV drugs, exemplified by diazepam and more recently by butorphanol, are considered to present a low potential for dependence or abuse. These drugs can be refilled, but only to a maximum of five times; the prescription is effective only for 6 months. Schedule V drugs, such as buprenorphine and diphenoxylate, have the lowest potential of abuse or dependence. Restrictions for drugs in this schedule are limited to age (humans), distribution by a pharmacist, and purchase in limited quantities. These drugs include selected antidiarrheals and antitussives.

Reporting Adverse Drug Reactions

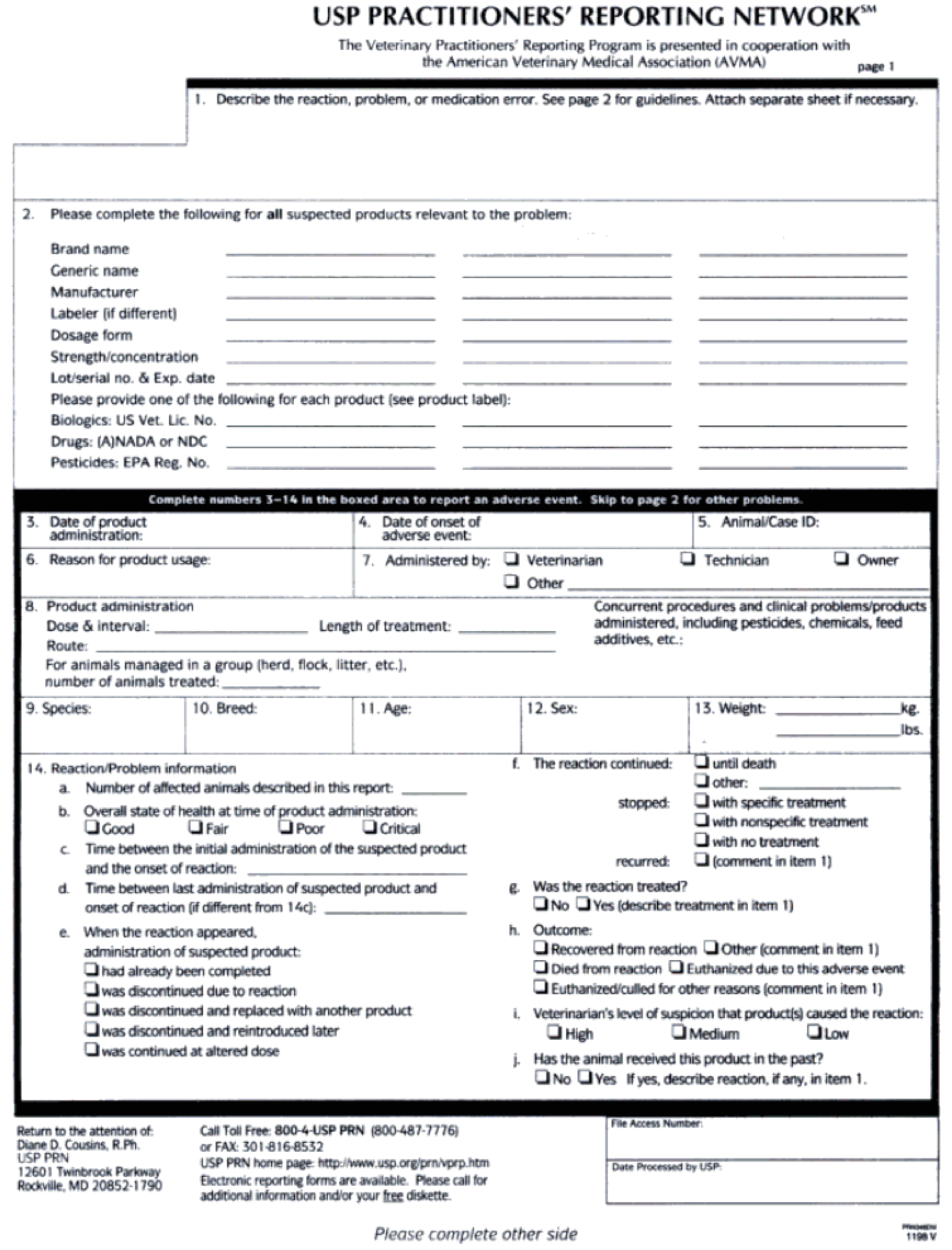
Adverse drug reactions have been described in this text. Report of adverse reactions is an important means of monitoring the safety of products as well as communicating unexpected adversities. In addition to the vehicles listed here, letters to the editors or case reports in veterinary journals or continuing education programs can be effective tools for reporting adverse drug reactions. Additionally, the adversity should be reported to the pharmaceutical company.

Center for Veterinary Medicine, Food and Drug Administration

Both veterinarians and animal owners are encouraged to report adverse drug reactions, adverse experiences, or product failures. Problems with animal drugs, devices, and foods can be reported to the FDA by submitting FDA Form 1932, *Veterinary Adverse Experience, Lack of Effectiveness or Product Defect Report*. The form is pre-addressed with postage prepaid. Reports are made to ADE

Table 5. Schedule Drugs

Schedule	Definition	Examples
I	Highest risk of abuse, dependence No medicinal use	Heroin, hallucinogens (LSD, mescaline, marijuana), amphetamines
II	High risk of abuse, dependence Limited medicinal use	Cocaine, morphine, meperidine, fentanyl, oxymorphone, pentobarbital, methylphenidate
III	Moderate potential for abuse, dependence Accepted therapeutic use	Selected opioids and barbiturates
IV	Low potential for abuse, dependence	Diazepam, chloral hydrate, chlordiazepoxide, phenobarbital, propoxyphene, anabolic steroids
V	Lowest potential for abuse	Buprenorphine, diphenoxylate



USP PRACTITIONERS' REPORTING NETWORK℠

The Veterinary Practitioners' Reporting Program is presented in cooperation with
the American Veterinary Medical Association (AVMA)

page 1

1. Describe the reaction, problem, or medication error. See page 2 for guidelines. Attach separate sheet if necessary.

2. Please complete the following for **all** suspected products relevant to the problem:

Brand name	______	______	______
Generic name	______	______	______
Manufacturer	______	______	______
Labeler (if different)	______	______	______
Dosage form	______	______	______
Strength/concentration	______	______	______
Lot/serial no. & Exp. date	______	______	______
Please provide one of the following for each product (see product label):			
Biologics: US Vet. Lic. No.	______	______	______
Drugs: (A)NADA or NDC	______	______	______
Pesticides: EPA Reg. No.	______	______	______

Complete numbers 3–14 in the boxed area to report an adverse event. Skip to page 2 for other problems.

3. Date of product administration:

4. Date of onset of adverse event:

5. Animal/Case ID:

6. Reason for product usage:

7. Administered by: ☐ Veterinarian ☐ Technician ☐ Owner ☐ Other ______

8. Product administration
Dose & interval: ______ Length of treatment: ______
Route: ______
For animals managed in a group (herd, flock, litter, etc.), number of animals treated: ______

Concurrent procedures and clinical problems/products administered, including pesticides, chemicals, feed additives, etc.:

9. Species:

10. Breed:

11. Age:

12. Sex:

13. Weight: ______ kg. ______ lbs.

14. Reaction/Problem information

a. Number of affected animals described in this report: ______

b. Overall state of health at time of product administration:
☐ Good ☐ Fair ☐ Poor ☐ Critical

c. Time between the initial administration of the suspected product and the onset of reaction: ______

d. Time between last administration of suspected product and onset of reaction (if different from 14c): ______

e. When the reaction appeared, administration of suspected product:
☐ had already been completed
☐ was discontinued due to reaction
☐ was discontinued and replaced with another product
☐ was discontinued and reintroduced later
☐ was continued at altered dose

f. The reaction continued: ☐ until death
☐ other: ______
stopped: ☐ with specific treatment
☐ with nonspecific treatment
☐ with no treatment
recurred: ☐ (comment in item 1)

g. Was the reaction treated?
☐ No ☐ Yes (describe treatment in item 1)

h. Outcome:
☐ Recovered from reaction ☐ Other (comment in item 1)
☐ Died from reaction ☐ Euthanized due to this adverse event
☐ Euthanized/culled for other reasons (comment in item 1)

i. Veterinarian's level of suspicion that product(s) caused the reaction:
☐ High ☐ Medium ☐ Low

j. Has the animal received this product in the past?
☐ No ☐ Yes If yes, describe reaction, if any, in item 1.

Return to the attention of:
Diane D. Cousins, R.Ph.
USP PRN
12601 Twinbrook Parkway
Rockville, MD 20852-1790

Call Toll Free: **800-4-USP PRN** (800-487-7776)
or FAX: 301-816-8532
USP PRN home page: http://www.usp.org/prn/vprp.htm
Electronic reporting forms are available. Please call for additional information and/or your free diskette.

File Access Number:

Date Processed by USP:

Please complete other side

[illegible]
1198 V

Figure 2. USP Practitioners' Reporting Network adverse drug reaction reporting form. (From the USP Practitioners' Reporting Network, 12601 Twinbrook Parkway, Rockville, MD 20852–1790.)

number because the decimal may be missed; a zero is always used to designate a fraction [e.g., 0.5] because the decimal may be missed) and the use of abbreviations that are similar (e.g., use of U for units [easily mistaken for a 0]). Writing numbers as words in lieu of or in addition to numerals may facilitate safety, particularly with toxic drugs.

Labels for prescription drugs should include the name, address, and phone number of the prescriber, the patient and owner's name (and, for controlled substances, address and phone number); animal name (if appropriate) and species; dispensing date; drug name, quantity, and strength; instructions for use; and appropriate precautionary statements. State regulations regarding the contents of the drug label may vary. Drugs should be dispensed in a childproof container unless requested otherwise by the owner; a signed request should be kept in the record if so requested.

ETHICAL CONSIDERATIONS IN CLINICAL TRIALS*

Assurance of Ethical Use of Animals

The use of animals in prospective research studies is becoming increasingly controversial. In this section, considerations for client-owned animals are contrasted with experimental animals that are owned by the research facility. Included in this latter group are animals that have been donated by clients. This section also discusses ethical consideration for humans, experimental animals, and client-owned animals in clinical trials. General ethical considerations for all clinical trials will also be presented.

Rights of Human Subjects

It is not unreasonable to expect the same concern and consideration for veterinary patients that is given human patients used as clinical research subjects. Human patients involved in clinical research are very well protected against inhumane use. The Nuremberg Code of Ethics in Medical Research (1948) emphasizes the rights of the experimental human subject. The Declaration of Helsinki (1964) as adopted by the World Medical Association went further and mandated that:

1. Such research must conform to scientific principles;
2. Design and performance of the research must be clearly formulated in a protocol; transmitted to a specially appointed, independent committee; and
3. Publication of results should accurately reflect the results of the study.

The Declaration emphasized the right of informed consent and specifically addressed human medical research that is combined with professional patient care. Research facilities such as academic institutions that direct clinical research in humans are guided by Institutional Review Boards whose primary charge is to ensure compliance with the Nuremburg Code and Declaration of Helsinki. With minor modifications, most of the guidelines delineated in these two documents also are applicable to the veterinary patient (client-owned animal) used in clinical research. Like human medical counterparts, veterinary clinical research facilities should institute a mechanism by which adherence to these guidelines is assured.

Welfare of Experimental Animals

Experimental animals are protected by guidelines offered by the Animal Welfare Act of 1966 and its subsequent amendments. The Public Health Service Policy (PHS) on Humane Care and Use of Laboratory Animals (i.e., the National Institutes of Health Policy) requires compliance with this act of all institutions receiving PHS funds. Most research facilities (academic institutions) have laboratory animal care committees which assure compliance by individual investigators with the PHS policy. However, these committees are not necessarily charged with the care of client-owned animals, and often (as at Texas A & M University) will agree that research involving client-owned animals does not fall under their purview.

Welfare of Client-Owned Animals

In order to protect the welfare of client-owned animals, some type of review board should be in place. In a University setting, a Hospital Review Committee (HRC) evaluates clinical trials and other types of clinical research (Boothe et al, 1992). The term HRC will be used in this manuscript to distinguish from Institutional Review Boards (IRB) that address human subjects in clinical research. The goals of an HRC should be: to protect the patient, client, institution and attending veterinarian(s) from the intended or inadvertent application of investigations that are inhumane or unethical; and to promote the advancement of science through clinical research. The HRC functions to safeguard the welfare of the patient through the approval of proposals involving clinical research. Although its mission is not to provide rigorous review of the scientific merits of a proposed study, decisions regarding the ethical nature of a proposed clinical trial may require the HRC to question the scientific basis and the scientific and statistical design of any proposals (Elliot, 1989).

General Ethical Considerations

General considerations on the ethical use of animals in clinical trials arise from the human research guidelines. Some of the following considerations are most applicable for clinical trials using client-owned animals. An overarching truth is that it is more ethical to perform a randomized clinical trial than to use treatments of unproven efficacy. The patient's best interest can not be forsaken for the sole purpose of "therapeutic progress"; rather, treatment of the patient is the priority. Completion of the trial must not be rushed if it creates risks to the patient. In the study design phase, protocols should be developed for use in the situation where the risk:benefit ratio of the therapeutic intervention becomes too high during the course of therapy (e.g., the trial will be terminated, the currently recom-

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*Excerpted from Boothe DM, Slater M: Proper implementation of clinical trials. In Dodds WJ (ed): Veterinary Medical Specialization: Bridging Science and Medicine, Advances in Veterinary Science and Medicine, vol 39. Orlando, Academic Press, 1995.

an adverse reaction occur or client withdrawal be desired. Relevant information that should be included in this section is as follows:

1. An explanation of whether compensation or treatment will be available if injuries occur;
2. A statement regarding the client's right to withdraw at any time with no change in patient care;
3. Who is to be contacted in the event of an adverse reaction/injury or if questions regarding the study arise;
4. Conditions that might lead the investigators to withdraw a patient from the study (e.g., noncompliance, poor record keeping or "escape criteria," such as a worsening of the disease being tested);
5. A statement regarding financial obligations of the client should his or her animal be withdrawn from the study; and
6. A statement allowing the client to seek a second opinion regarding the cause of death should his or her animal die while participating in the study.

The fifth paragraph ensures the confidentiality of the study. Points to be included are:

1. A statement that assures that the data collected from the animal will be kept confidential;
2. A statement regarding notification of findings that might affect the willingness of the client to continue participation;
3. A statement regarding notification of the results of the study upon its completion; and
4. A statement verifying that the client has participated in this study willingly.

Each page of the informed consent should be numbered and accompanied by a place for the client's initials next to the number.

Informed consent may be *waived* under extenuating circumstances if the investigator and an unbiased clinician (one not particpating in the study) certify in writing all of the following:

1. The patient is confronted with a life-threatening situation that necessitates the use of the intervention being tested;
2. Informed consent cannot be obtained from a legal representative of the patient (i.e., stray animals);
3. There is not sufficient time to obtain informed consent from the patient's legal representative; and
4. There is no alternative method of approved or generally recognized therapy that provides an equivalent or greater likelihood of saving the patient's life.

REPORTING AND REVIEWING CLINICAL TRIALS

Data Reporting

A clinical trial is not complete until the information is disseminated. Publications of results should be prepared and made available as soon as possible. Although most manuscripts are prepared after closeout, in certain instances interim publications are prepared.

Interim publications provide access to study results as they occur. Additional benefits might include easier preparation of the final manuscript and greater exposure of the study to the public. However, there are several disadvantages to interim reporting (Meinert, 1986). Results that are inconclusive may be confusing. If the results are discouraging, investigator enthusiasm may wane. Most critical is the possibility of bias in subsequent treatment assignment and data collection. Finally, data analysis and presentation may differ from and thus diminish the impact of the final report. Results of the study can be disseminated through publications in peer-reviewed journals and presentations at national meetings. Some journals (those that focus predominantly on human medicine) will not publish papers that have been presented nationally. The time gap between presentation and publication should be minimal. The choice of journal should be limited to referred journals that are covered in *Index Medicus* and *Index Veterinarius*. Unreferred journals should be avoided if they lack a critical review process. Such journals may reach a smaller public and thus may be more difficult for other investigators to identify or retrieve. A specialty journal (i.e., *Internal Medicine, Neurology,* or *Surgery*) might be considered if the results are of primary interest to the specialty group.

The potential importance of many veterinary clinical trials is not realized because of failure to publish the appropriate information. The goal of the publication should be to provide a clear, concise description of the study (Meinert, 1986). Studies that report nonstatistically significant findings should also be published. The clinical trial may only result in a single manuscript that is published upon completion of the trials. The organization of the manuscript will vary with the targeted journal. Typical components include the following.

The *title* is one of the most important components of the publication. It should be concise and as short as possible while indicating the main thrust of the paper. The term *clinical trial* should be included in the title. The title section should also include the authors, source of financial support, acknowledgements, and address for reprints. Finally, a list of key words selected by the author should be included to allow for retrieval.

The *abstract* is often the only part of a paper that is read and as such should provide a summary of the paper. The abstract will be included in Medline, the computerized version of *Index Medicus*, or other computerized databases. The abstract should include the study purpose or objective; primary outcome measure; intervention; type of control; method of allocation; blinding procedures; number of animals enrolled and studied; and conclusions.

The *introduction* should be short and succinct. Its purpose is to provide a historical background for the study. Included is a literature review; what led to the initiation of the study; the study objectives; and the rationale for the study. This might include a rationale for the study design, intervention, or outcome measurements.

The *methods section* should be sufficiently detailed to allow readers to make informed judgments regarding the quality of the methods. Citation of a previously published paper describing the methods can reduce the content if the paper was devoted primarily to the design and methods of the trial.

The *results section* is generally the longest. The crux of the paper should be represented by tables, charts, and figures, which should be understandable without reference to the text.

The *discussion* should highlight the important findings of the study. Positive as well as negative findings should be reported. The clinical implications of these results and consistency with previous findings should be discussed.

The *conclusion* may either stand alone or complete the discussion. The conclusions must be drawn from the results of the trial. If appropriate, the statistical power of the study should be noted if the conclusion favors the null hypothesis. Finally, a statement regarding the extent of generalization should be included.

References should be limited to those that support the rationale of the objectives and document methods of data collection and analysis. The journal of publication will dictate the organization of the references. Original articles should be referenced whenever possible. Secondary sources are acceptable if the primary cannot be found; if the primary is published in a foreign language; or if the secondary expands on information provided by the primary paper. Checks of accuracy of title name, spelling of author's name, and so forth should be based on the article itself and not on citations listed in other bibliographies (e.g., Medline).

The *appendix section* is optional and may not be allowed by some journals. Contents should be limited to information regarding methods that is too technical or detailed to include in the body of the text. Examples of information to be contained in the appendices are details of sample size calculations; sample data forms; data collection schedules; special charts, figures, equations; consent statements; and data listings.

The submission process can be facilitated if the manuscript is reviewed before submission. Authors should review the paper for inconsistencies in format and style (including tables and figures), for redundancy, and for reporting deficiencies. Figure and table numbers should match text citations. Citations should be reviewed to ensure that information cited is correct. Colleagues should provide the second review. Their primary function is to identify confusing aspects of the manuscript. Total rewrites may result from this internal review. The final review by the authors should focus on the format of the journal to which the manuscript is to be submitted. The number of copies and prints submitted, title page, style and format, and so forth, should match the specifications set forth in the journal's "Instructions to Authors." After publication, the primary authors should establish an archive consisting of all documents related to the paper, beginning with raw data and finishing with a copy of the printed manuscript. This information should be kept at least 3 years (Meinert, 1986).

Reviewing a Clinical Trial

When reviewing a manuscript that reports the results of a clinical trial, the reviewer should be unbiased regarding the results. The reviewer's opinion should be based on the merits of the study rather than on the opinions and critiques of others. The purpose of the clinical report should be strongly considered, particularly if sponsor support was critical to the study and the sponsor stands to gain financially from it. The information provided in the report should allow adequate review of methodology so that critical aspects of the report can be evaluated. Reproducibility of results and generalization of results to a large population (rather than a small subset) should be assessed. Exclusion of patients should be well justified. The study design should be well safeguarded against biases during the assignment and administration of the intervention and during data collection and analysis. Methods used to edit the data for errors or inadequacies should be cited. Statistical methods should be appropriately sophisticated. Major differences in baseline group comparability, dropout rates, or compliance should be evaluated for a possible role in treatment differences.

Table 2. Equivalents

		Approximate
1 grain (gr)	64.8 milligram (mg)	60 mg
1 ounce (oz)	28.35 gram (g)	30 g
1 pound (lb)	453.6 g	454 g
1 dram (60 gr)	3.9 g	4 g
1 apothecary ounce (480 gr)	31.1 g	30 g
1 minim	0.06 (mL) milliliter	0.06 mL
1 fluid dram	3.7 mL	4 mL
1 fluid ounce	29.573 mL	30 mL
1 pint	473.1 mL	480 or 500 mL
1 gallon	3785.4 mL	4000 mL
1 mg	1/64.8 gr	1/65 or 1/60 gr
1 g	15.432 gr	15 gr
1 kilogram (kg)	2.2 pounds (lb)	
1 gallon (water)	8.337 lb (8 lb approx.)	3.8 kg (approx.)
1 gallon occupies 231 cubic inches		
1 mL	1.000027 cubic centimeters	
1 pint	473 mL	500 mL
1 quart	946 mL	1000 mL
1 drop	0.06 mL	1 minim
1 dessertspoonful		8 mL
1 teaspoonful (tsp)		5 mL
1 tablespoonful (tbs)		15 mL

Table 3. Conversions for Calculating Dosage

w/v %	**mg/mL**	**μg/mL (mcg/mL)**	**Dilution g to mL**
10%	100	100,000	1:10
5%	50	50,000	1:20
2%	20	20,000	1:50
1%	10	10,000	1:100
0.1%	1	1,000	1:1,000
0.02%	0.2	200	1:5,000
0.01%	0.1	100	1:25,000
0.004%	0.04	40	1:25,000
0.002%	0.02	20	1:50,000
0.001%	0.01	10	1:100,000
0.001%	0.001	1	1:1,000,000

Table 4. Dry Weight and Volume Conversions

1 pound (lb)	453.6 grams (g)
1 gram (g)	0.0022 pound (lb)
1 gram (g)	1000 milligrams (mg)
1 gram (g)	1,000,000 micrograms (μg)
1 kilogram (kg)	1000 grams (g)
1 kilogram (kg)	2.205 pounds (lb)
1 milligram (mg)	0.001 gram (g)
1 milligram (mg)	1000 micrograms (μg)
1 microgram (μg)	0.001 milligram (mg)
1 microgram per gram (μg/g)	1 part per million (ppm)
1 part per million (ppm)	0.454 milligram/pound (mg/lb)
1 part per million (ppm)	0.907 gram per ton (g/T)
1 liter (L)	1000 milliliter (mL)
1 milliliter (mL)	1000 microliter (μL or lambda)

Consider the following example: What is the equivalent weight, in grams, of NaCl, HCl, and H_2SO_4?

NaCl	**HCl**	**H_2SO_4**
Na = 23	H = 1	$H_2 = 2$
Cl = 35	Cl = 35	$SO_4 = 32 + 4(16) = 96$
Total = 58	Total = 36	Total = 98
Valence = 1	Valence = 1	Valence = 2
Equivalent weight = 58	Equivalent weight = 36	Equivalent weight = 49

Normality

Normality is the number or gram equivalent weight per liter of solution. An equivalent weight is equal to the molecular weight of a substance (see table below) divided by its valence. The valence of a molecule is the number of units that can combine with or replace 1 M of hydrogen ions. Normality is not a commonly used expression; rather, milliequivalents per liter (mEq/L) or millimoles per liter (mmol/L) is used to express electrolyte concentrations.

Molecule	Abbrev	Valence	GMW
Barium	Ba		137
Bromide	Br	1	80
Carbon	C		12
Calcium	Ca	2	40
Chloride	Cl	1	35.5
Copper	Cu		63.5
Fluoride	F		19
Gold	Au		108
Hydrogen	H	1	1
Iron	Fe		55.8
Lead	Pb		207
Lithium	Li		6.9
Magnesium	Mg	2	24
Nitrogen	N		14
Oxygen	O	1	16
Phosphorus	P		31
Potassium	K	1	39
Sodium	Na	1	23
Sulfur	S		32
Zinc	Zn		65

Vitamin B_{12}: cobalamin (minimally absorbed)	Dietary form (must be activated)	DNA synthesis; facilitates folic acid metabolism	Cyclical structure similar to hemoglobin, with cobalt rather than iron in center. Deficiencies rare (see text) but result in *combined systems disease* or pernicious anemia that targets gastrointestinal tract, blood cells, and neurologic system.
Vitamin C (water soluble): ascorbic acid		Reducing agent, serving as an electron donor for enzymatic reactions, especially hydroxylation and amidation. Synthesized in most mammals (exceptions: humans and other primates, guinea pigs). Particularly important for collagen synthesis, conversion of lysin to carnitine, and folic acid to folinic acid; converts ferric iron to ferrous iron, assisting iron absorption from gastrointestinal tract. Antioxidant	Few scientific studies support claims regarding prevention or treatment of cardiac disease or cancer
Vitamin D (fat soluble)	Ergocalciferol: vitamin D_2 Cholecalciferol: vitamin D_3 25-Hydroxycholecalciferol: calcifediol 1,25-Dihydroxycholecalciferol: calcitriol (vitamin D_2) Dihydrotachysterol (isomer of vitamin D_2)	Calcium metabolism, hematopoiesis, cell differentiation, regulation of insulin secretion	Excessive consumption may result in hypercalcemia, anorexia, nausea, vomiting, polyuria, thirst, muscular weakness, joint pains, and bone demineralization
Vitamin E (fat soluble)	Tocopherols (alpha and gamma) and tocotrienols	Free radical scavenger, preventing oxidation of polyunsaturated fatty acids and thiol-rich proteins in cell membranes; T-lymphocyte maturation; decreased oxidation of low-density lipoproteins; protects against free radical damage to retina and nervous system	Overdosing may interfere with vitamins A and K absorption; bleeding disorders may occur
Vitamin K	Phylloquinone (chlorophyll-containing plants) Menaquinones (bacteria)	Activates clotting factors VII, IX, and X	

Data from Atkinson RL: Nutritional aspects of pharmacology. In Brody TM, Larner JL, Minneman KP (eds): Human Pharmacology: Molecular to Clinical, pp 843–860. Mosby, St. Louis, 1998.

Table 2. Selected Activated Charcoal Products

Name	Properties	Manufacturer	Address
Acta-Char	Activated charcoal powder, USP, 30 g in wide-mouth plastic bottle (400-mL capacity)	Med-Corp, Inc.	5310 Harvest Hill Road Dallas, TX 75230
Activated charcoal, USP	Activated charcoal powder, USP, 30 g in 8-oz wide-mouth plastic jar (unit dose) 120 g in 16-oz wide-mouth jar 240 g in 32-oz wide-mouth jar	Humco Laboratories	1008 Whitaker Texarkana, TX 75504
Activated charcoal, USP	Activated charcoal powder, USP, 454 g (1 lb) in wide-mouth jar	Mallinkrodt, Inc.	Box M Paris, KY 40361
Activated charcoal, USP, in liquid base	Activated charcoal, USP, in liquid base containing water and propylene glycol (amount of propylene glycol unspecified) 12.5 g in 60-mL wide-mouth bottle 25 g in 120-mL squeeze bottle with spout 50 g in 240-mL squeeze bottle with spout	Bowman Pharmaceuticals, Inc.	119 Schroyer Ave, SW Canton, OH 44702
CharcoAid		Requa Mfg. Co.	1 Seneca Place Greenwich, CT 06830
Charcolantidote	Activated charcoal powder, USP 15-g bottle (150-mL capacity) 30-g bottle (200-mL capacity)	U.S. Products, Inc.	16636 NW 54th Ave Miami Lakes, FL 33014
Insta-Char	Activated charcoal, USP, in aqueous suspension (water is the sole liquid ingredient) 15 g in 120-mL squeeze bottle with spout 50 g in 250-mL squeeze bottle with spout	Frank W. Kerr Chemical Co.	43155 SW Nine Mile Road Northville, MI 48167
Liquid-Antidose	Activated charcoal, USP, in liquid base containing carboxymethylcellulose, sodium benzoate (preservative) and water 40 g in liquid base, 200 mL	U.S. Products, Inc.	16636 NW 54th Ave Miami Lakes, FL 33014
Norit USP XX	Activated charcoal powder, USP, in bulk 15-kg containers (Norit USP XX is the activated charcoal used in all products listed above)	American Norit Co.	6301 Glidden Way Jacksonville, FL 32201
Poison Antidote Kit	1. Activated charcoal, USP, in liquid base containing water and propylene glycol (amount of propylene glycol unspecified). 4 bottles, 12.5 g each of activated charcoal in liquid base, 60 mL 2. 1 bottle, ipecac syrup, 30 mL	Bowman Pharmaceuticals, Inc.	119 Schroyer Ave, SW Canton, OH 44702
Toxiban	Granules, 47% activated charcoal, 10% kaolin, 42% wetting and dispensing agents; 5-kg pail Suspension, 10.4% activated charcoal, 6.25% kaolin in an aqueous dose; 240-ml bottle	Vet-A-Mix	604 W Thomas Ave Shenandoah, IA 51601

Abbreviations: USP = United States Pharmacopeial Convention.
Adapted from Activated charcoal products for medicinal (antidote) use. Vet Hum Toxicol 1983; 25: 294.

Table 3. Toxic Agents or Drugs and Antidotes or Treatments

Toxic Agent	Systemic Antidote	Dosage and Method for Treatment
Acetaminophen and phenacetin	*N*-Acetylcysteine (Mucomyst, Mead Johnson)	150 mg/kg loading dose, PO or IV, then 50 mg/kg q4h for 17–20 additional doses
Acids and alkali (household cleaning products, toilet bowl and drain cleaners, dishwater detergents, cleaners, antirust compounds, alkaline batteries)	No specific antidote	Emesis and gastric lavage are contraindicated; if minimal esophageal injury, lavage with aluminum hydroxide may be helpful with acid ingestions. Supportive therapy includes fluid therapy
	Acids	Weak alkali: magnesium oxide solution (1:25 warm water) internally. *Never give sodium bicarbonate!* Milk of magnesia: 1–15 mL. Flush externally with water. Apply paste of sodium bicarbonate
	Alkalis	Weak acid: vinegar (diluted 1:4), 1% acetic acid or lemon juice given PO. Dilute albumin (4–6 egg whites to 1 qt warm water) or give whole milk followed by activated charcoal and then a cathartic because some compounds are soluble in excess albumin Local: flush with copious amounts of water and apply vinegar
Alkaloids		Potassium permanganate (1:5000 to 1:10,000) for lavage or PO administration. Tannic acid or strong tea (200–500 mg in 30–60 mL of water) except in cases of poisoning by cocaine, nicotine, physostigmine, atropine, and morphine. Emetic or purgative should be used for prompt removal of tannates
Amitraz	Atipamazole	50 µg/kg IM. Signs should reverse in 10 min. Repeat every 3 to 4 hours as needed. Can follow with 0.11 mg/kg (D) to 0.5 mg/kg (C); Yohimbine slow IV every 6 hours.
Amphetamines	Chlorpromazine	1 mg/kg IM, IP, IV; administer only half dose if barbiturates have been given: blocks excitation. Higher doses (10–18 mg/kg IV) may be beneficial if large volumes are consumed. Treatment of increased intracranial pressure may be indicated (mannitol, furosemide)
	Urinary alkalinization ammonium chloride	100–200 mg/kg/day divided q8–12h (contraindicated if myoglobinuria, renal failure, or acidosis is present)
Antihistamines	No specific antidote	
Antitussives	Naloxone	If narcotic (e.g., hydrocodone, codeine)
Arsenic, mercury, and other heavy metals except cadmium, lead, silver, selenium, and thallium (see also specific metals)	Sodium thiosulfate (arsenic)	10% solution given PO (0.5–3.0 g for small animals. Followed by lavage or emesis. Protein (e.g., evaporated milk, egg whites). Tannic acid or strong tea. Sodium nitrite is used in humans to convert hemoglobin to oxidized methemoglobin, which has a very high affinity for cyanide. Sodium thiosulfate facilitates thiocyanate formation. Alternative treatment may include hydroxycobalamin, which reacts with cyanide to form cyanocobalamin
	Dimercaprol (BAL, Hynson, Wescott & Dunning)	10% solution in oil; give small animals 2.5–5.0 mg/kg IM (0.025–0.05 mg/kg) q4h for 2 days, twice daily for the next 10 days or until recovery **NOTE:** In severe acute poisoning 5 mg/kg dosage should be given only for the first day
	D-Penicillamine (Cuprimine, Merck & Co.)	Developed from chronic mercury poisoning, now seems most promising drug; no reports on dosage for animals. Dosage for humans is 250 mg PO q6h for 10 days (3–4 mg/kg)
	Succimer (mesodimercaptosuccinic acid, DMSA) (Chemet; McNeil Consumer Products, a division of McNeil-PPC, Inc., Fort Washington, PA 19304)	10 mg/kg PO q8h for 10 days
	N-acetylcysteine (Mucomyst, Mead Johnson)	140–280 mg/kg PO, then 70 mg/kg PO q6h for 3 days (IV administration okay in vomiting dogs)
Aspirin	No specific antidote (see also nonsteroidal anti-inflammatory drugs)	Acute toxicosis: urinary alkalinization, other supportive therapy. Doses of 50 mg/kg/day (dog) and 25 mg/kg/day (cat); 7 mL/kg/day of bismuth subsalicylate (dogs and cats) may be toxic. Toxic concentrations in humans
Atropine, belladonna alkaloids	Physostigmine salicylate	0.1–0.6 mg/kg (do not use neostigmine)
Barbiturates	Doxapram (Dopram)	2% solution: give 3–5 mg/kg IV only (0.14–0.25 mL/kg) repeated as necessary. Alkalinize urine.
Barium, bismuth salts	Sodium sulfate/magnesium sulfate	20% solution given PO. Dosage: 2–25 gm

Table continued on following page

Table 3. Toxic Agents or Drugs and Antidotes or Treatments *Continued*

Toxic Agent	Systemic Antidote	Dosage and Method for Treatment
Bleach	Treat as alkali	Use of emetics controversial; treat as an alkali poisoning. Therapies have included milk or water (large volumes), milk of magnesia (2–3 mL/kg), egg whites, or powdered milk slurry. Sodium bicarbonate not recommended
Borates (roach killers, flea products, fertilizers, herbicides, antiseptics, disinfectants, contact lens solutions)	No specific antidote	Supportive therapy includes emetics and gastric lavage, fluid therapy and diuresis, treatment of seizures and hyperthermia as indicated
Bromethalin	No specific antidote	Supportive care may include treatment of cerebral edema
Bromides	Chlorides (sodium or ammonium salts)	0.5–1.0 g daily for several days; hasten excretion
Botulism	Antitoxin	Use is controversial. Supportive care may be sufficient. Supportive therapy may include penicillin, physostigmine or neostigmine, and atropine
Caffeine	See Chocolate	
Carbon monoxide	Oxygen	Pure oxygen at normal or high pressure; artificial respiration; blood transfusion
Carbon tetrachloride		Acacia or gum arabic as mucilage. Empty stomach, give high protein and high carbohydrate diet; maintain fluid and electrolyte balance. Hemodialysis is indicated in anuria. Epinephrine is contraindicated (ventricular fibrillation!)
Chocolate (theobromine)	Metaprolol or propranolol	Not a specific antidote. Metaprolol: Dog: 0.5–1 mg/kg PO q8h; cat: 12.5–25 mg/cat PO q8–12h. With caution: 0.04–0.06 mg/kg IV q8h. Propanolol: 0.02–0.06 mg/kg IV over several minutes if acute; nonacute: 2.5–10 mg/kg (dogs) PO q8–12h; 2.5 to 5 mg/cats PO q8–12h. Supportive therapy may include atropine; lidocaine 1–2 mg/kg IV bolus followed by 25–75 µg/kg/min IV infusion (dogs) or 0.25–1 mg/kg IV bolus followed by 5–40 µg/kg/min IV infusion (cats)
Cholinergic agents	Atropine sulfate	0.02–0.04 mg/kg, as needed
Cholinesterase inhibitors: malathion, parathion, diazinon, carbaryl, bendiocarb, propoxur, chlorpyrifos, methylcarbamate, chlorfenvinphos, cythioate, dichlorvos, dioxathion, fenthion, ronnel, phosmet, disulfoton, flybait (Golden Malrin)	Atropine sulfate	Dosage is 0.2–0.4 mg/kg, repeated as needed for atropinization. Repeat in decreasing doses (cut by half). Treat cyanosis or dyspnea (oxygen) first, if present. Atropine blocks only muscarinic effects. Atropine in oil may be injected for prolonged effect during the night. *Avoid atropine intoxication!* Organophosphate inhibition tends to be irreversible; organocarbamate tends to be reversible
	Pralidoxime chloride (2-PAM)	5% solution; 20–50 mg/kg IM or by slow IV (0.2–1.0 mg/kg) injection (maximum dose is 500 mg/min), repeat as needed 2–3 times. Do not treat again if no effect. 2-PAM alleviates nicotinic effect and regenerates cholinesterase. Morphine, succinylcholine, and phenothiazine tranquilizers are contraindicated
	Diphenydramine	1–4 mg/kg IM, PO q8h. To block nicotinic effects
Cocaine	No specific antidote	Chlorpromazine (up to 15 mg/kg; may lower seizure threshold, use cautiously); butylcholinesterase may convert cocaine to inactive metabolites (currently under investigation); fluids; metoprolol or propanolol to treat cardiac arrythmias (see Chocolate); phentolamine or sodium nitroprusside if β-blockers cause hypertension; lidocaine (in lieu of β-blockers to control cardiac arrhythmias; see Chocolate)
Copper (see also Arsenic)	Sodium ferrocyanide	In water (0.3–3.5 g for small animals). Albumin (see Alkali or Acids). For acids: magnesium oxide (see Acids)
	D-Penicillamine (Cuprimine)	52 mg/kg for 6 days (also see Arsenic)
Coumarin-derivative anticoagulants	Vitamin K, (AquaMEPHYTON, 5-mg capsules, Merck & Co., Vita K_1, Eschar, 25-mg capsules)	Give 3–5 mg/kg/day with canned food. Treat 7 days for warfarin-type, treat 21–30 days for second-generation anticoagulant rodenticides. PO therapy is more efficacious than IV
	Whole blood or plasma	Blood transfusion, 25 mL/kg
Crayons (aniline dyes)	Ascorbic acid	20–30 mg/kg PO or 20 mg/kg IV slowly
	Methylene blue (if ascorbic acid fails)	Dogs: 3–4 mg/kg IV; see also sodium nitrate and sodium thiosulfate under methemoglobinemia-producing agents
		Cats: 1.5 mg/kg (note that methylene blue may cause Heinz body formation in the absence of methemoglobinemia)

Table 3. Toxic Agents or Drugs and Antidotes or Treatments *Continued*

Toxic Agent	**Systemic Antidote**	**Dosage and Method for Treatment**
Curare	Neostigmine methylsulfate	Solution: 1:5000 for 1:2000 (1 mL = 0.2–0.5 mg/mL). Dose is 0.005 mg/5 kg, SC. Follow with IV injection of atropine (0.04 mg/kg)
	Edrophonium chloride (Tensilon, Roche), artificial respiration	1% solution; give 0.05–1.0 mg/kg IV
Cyanide	Methemoglobin (sodiun nitrite is used to form methemoglobin)	1% solution of sodium nitrite, dosage is 16 mg/kg IV (1.6 mL/kg). Sodium nitrate is used in humans to convert hemoglobin to oxidized hemoglobin, which has a very high affinity for cyanide.
	Sodium thiosulfate	Follow with sodium thiosulfate 20% solution at dosage of 30–40 mg/kg (0.15–0.2 mL/kg) IV. If treatment is repeated, use only sodium thiosulfate. Sodium thiosulfate facilitates thiocyanate formation. **NOTE:** Both of the above may be given simultaneously as follows: 0.5 mL/kg of combination consisting of 10 g sodium nitrite, 15 g sodium thiosulfate, distilled water q.s. 250 mL. Dosage may be repeated once. If further treatment is required, give only 20% solution of sodium thiosulfate at level of 0.2 mL/kg Other therapies that may be useful: hydroxycobalamin (investigational, not available in United States); dicobalt edetate (forms nontoxic stable complex with cyanide; not available in United States); amyl nitrate (in humans; use not documented in dogs and cats)
Decongestants	No specific antidote	
Detergents: anionic (Na, K, NH_4^+ salts)		Milk or water followed by demulcent (oils, acacia, gelatin, starch, egg white)
Detergents: cationic (chlorides, iodides)		Soap (castile) dissolved in 4 times its bulk of hot water. Albumin (see Alkali)
Diatomaceous earth		No treatment indicated unless pulmonary. Then supportive
Digitalis glycosides, oleander, and *Bufo* toads	Potassium chloride	Dog: 0.5–2.0 g PO in divided doses or, in serious cases, as diluted solution given IV by slow drip (ECG control is essential)
	Diphenylhydantoin	25 mg/min IV until control is established
	Propranolol (β-blocker)	0.5–1.0 mg/kg IV or IM as needed to control cardiac arrhythmias (ECG control is essential)
	Atropine sulfate	0.02–0.04 mg/kg as needed for cholinergic control
Dinoseb (dinitrophenol)	No specific therapy	Atropine may contribute to hyperthermia and may be contraindicated. Supportive therapy
Diquat Bromide	No known antidote	Supportive therapy should include fluid therapy, treatment for acute renal failure; experimental therapies have included niacin, riboflavin, ascorbic acid, superoxide dismutase, and *N*-acetylcysteine
Ethylene glycol	Ethanol	See Methanol and Ethlene Glycol. Minimal lethal dose of ethylene glycol is 4.2–6.6 mL/kg (4.5 oz in 20-lb dog) and 1.5 mL for cats. Give IV, 1.1 g/kg (4.4 mL/kg) of 25% solution. Give 0.5 g/kg (2.0 mL/kg) q4h for 4 days. To prevent or correct acidosis, use sodium bicarbonate IV, 0.4 g/kg. Activated charcoal: 5 g/kg orally if within 4 h of ingestion
	4-Methylpyrazole	20 mg/kg, 15 mg/kg at 12 and 24 h, 5 mg/kg at 36 h
	Sodium bicarbonate 5%	8 mL/kg (dog) or 6 mg/kg (cat) IP q4h for 5 treatments, then q6h for 4 more treatments
Fertilizer	No specific antidote	Supportive therapy may include treatment for electrolyte disorders (monitor); vomiting (antiemetics); H_2-receptor blockers for gastritis; sucralfate and analgesics (as needed)
Fluoride	Calcium borogluconate	3–10 mL of 5%–10% solution. Calcium (milk, limewater, or powdered chalk mixed with water) given PO
Fluoracetate (Compound 1080, Sigma)	Glyceryl monoacetin	0.1–0.5 mg/kg IM hourly for several hours (total 2–4 mg/kg); or diluted (0.5%–1.0% IV) (danger of hemolysis). Monoacetin is available only from chemical supply houses
	Acetamide	Animal may be protected if acetamide is given before or simultaneously with Compound 1080 (experimental)
	Pentobarbital **NOTE:** All treatments are generally unrewarding	May protect against lethal dose (experimental)

Table continued on following page

Table 3. Toxic Agents or Drugs and Antidotes or Treatments *Continued*

Toxic Agent	Systemic Antidote	Dosage and Method for Treatment
Penitrem A (neurotoxin in moldy food, garbage, nuts)	No specific antidote	Acepromazine has been recommended to control tremors, although lowered seizure threshold may cause seizures. IV methocarbamol or diazepam also may be helpful
Pennyroyal oil	No specific antidote	Treatment should focus on supporting hepatic failure, prevention or treatment of seizures
Petroleum distillates (aliphatic hydrocarbons)		Give olive oil, other vegetable oils, or mineral oil orally. After 1/2 hour, give sodium sulfate as cathartic. Emesis and lavage are contraindicated for ingested volatile solvents, but petroleum distillates are used as carrier agents for more toxic agents
Phenolics	No known antidotes	*N*-acetycysteine indicated for renal or hepatic damage
Phenols and cresols		Soap-and-water or alcohol lavage of skin: sodium bicarbonate (0.5%) dressings. Give activated charcoal and/or mineral oil orally
Phenothiazine	Methamphetamine (Desoxyn 7, Abbott)	0.1 to 0.2 mg/kg IV; also transfusion. Only available in tablet form
Phosphorus	Supportive therapy	Copper sulfate (0.2 to 0.4% solution) or potassium permanganate (1:5000 solution) for lavage. Turpentine (preferably old oxidized) in gelatin capsules or floated on hot water. Give 2 ml 4 times at 15-minute intervals Activated charcoal Do not give vegetable oil cathartic. Remove all fat from diet
Phosphate (sodium) enemas	Calcium gluconate (10%)	Supportive therapy should target correction of electrolyte imbalances, treatment of hypocalcemic tetany, and administration of magnesium sulfate if calcium therapy does not control tetany 0.5 to 1.5 ml/kg IV slowly over 30 minutes; monitor ECG for prolongation of Q-T interval or bradycardia or other dysrhythmias. If animal has not responded in 1.5 hr, alternative therapy should be implemented.
Phytotoxins and botulin. Examples of phytotoxins: ricin, abrin, robin, crotin	Antitoxins not available commercially	As indicated for specific antitoxins.
Pine oils	No specific antidotes	
Pyrethrins, pyrethroids: allethrin, fenvalerate, resmethrin, sumethrin, permethrin, cypermethrin, tetramethrin, cyfluthrin, tralomethrin, pallethrin	No specific antidotes	Supportive therapy may include treatment of anaphylaxis, atropine (not a specific antidote: indicated only to control parasympathetic signs), fluids, and muscle relaxants such as methocarbamol
Red squill	Atropine sulfate, propranolol, potassium chloride	See Digitalis
Scorpion sting	Antivenin not recommended	Supportive therapy includes analgesia to control pain (morphine and meperidine but not butorphanol are contraindicated due to potential synergy with scorpion venom); methocarbamol if muscle spasms evident; fluid therapy
Silver nitrate		Normal saline for lavage. Albumin
Smoke inhalation	Supportive therapy	Supportive therapy should target the respiratory system and treatment of carbon monoxide poisoning: oxygen therapy; intermittent positive-pressure ventilation with positive end-expiratory pressure with positive inotropic support, bronchodilators, treatment for cyanide poisoning if indicated, and treatment of cerebral edema
Snake bite		
Rattlesnake, copperhead, water moccasin	Antivenin (Wyeth), Trivalent Crotalidae (Fort Dodge)	Caution: equine origin. Administer 1–2 vials, IV, slowly, diluted in 250–500 mL of saline or lactated Ringer's solution. Also administer antihistamines. *Corticosteroids are contraindicated*
Coral snake	Antivenin (Micrurus fulvius) (Wyeth)	Caution: equine origin. May be used as with pit viper antivenin
Spider bite		
Black widow (neurotoxin)	Antivenin (Latrodectus mactans) (Merck & Co.)	Caution: equine origin. Administer IV undiluted. Supportive therapy should include muscle relaxants (dantrolene or methocarbamol), analgesics, calcium gluconate for severe muscle cramping
	Dantrolene sodium (Dantrium, Norwich-Eaton)	1 mg/kg IV, followed by 1 mg/kg per os q4h
Brown Recluse	Dapsone	1 mg/kg twice daily for 10 days (to minimize necrosis). Other supportive therapy includes hyperbaric oxygen therapy (at 1–2 atmospheres twice daily for 3 days), colchicine, treatment of intravascular hemolysis, fluid therapy

APPENDIX 6

Generic and Trade Names

Table 1. Generic and Trade Names

Generic	Trade Name
Acarbose	Precose
Acemannan	Carrisyn
Acetaminophen	Datril
Acetaminophen	Tylenol, Banesin
Acetic acid	Vinegar
Acetazolamide	Diamox
Acetohydroxamic acid	Lithostat
Acetylcysteine	Mucomyst, Mucosil
Acetylsalicylic acid	Aspirin
Acepromazine	ProMACE
Actinomycin D	Cosmegen
Activated charcoal	Requa, Actidose-Aqua; see Appendix 5
Albendazole	Valbazen
Albuterol	Proventil, Ventolin
Alfentanil	Alfenta
Allopurinol	Zyloprim
Aloe vera cream	Dermaide, Aloe
Alprazolam	Xanax
Althesin*	
Aluminum hydroxide	Amphojel, ALternaGEL, Cremaline, Basaljel
Amikacin	AMIGLYDE-V, Amikin
Aminocaproic acid	Amicar
Aminopentamide hydrogen sulfate	Centrine
Aminophylline	Somophyllin
Aminopromazine	Tetrameprozine
4-Aminopyridine	
Amitraz	Mitaban, Point-Guard
Amitriptyline HCl	Amitril, Elavil
Amlopidine besylate	Norvasc
Ammonium chloride	Uroeze (assoc. w/methionine)
Amoxicillin	Amoxi-Drops, Amoxi-Tabs, Amoxi-bol
Amoxicillin sodium salt	
Amoxicillin/clavulanic acid	Clavamox
Amphetamine SO_4	Benzedrine, Delcobese
Amphotericin B	Fungizone
Amphotericin B lipid complex	Ambelcet
Amphotericin B lipid complex	AmBisome
Amphotericin B	Amphotec
Ampicillin	Omnipen, Polycillin, Principen, Polyflex
Ampicillin trihydrate	Polyflex, Principen
Ampicillin sodium salt	Omnipen-N, Amp-Equine
Amprolium	CORID
Amrinone	Inocor
Antazoline 0.5%	Opcon-A
Antivenin Coral Snake	Antivenin (Micrurus fulvius)
Antivenin Crotalidae	Antivenin (Crotalidae) polyvalent
Apomorphine	Apomorphine tablets
Ascorbic acid	Ascorbicap, Cebione, Cecon, Vitamin C
Asparaginase	Elspar
Atenolol	Atenolol, Tenormin
Atipamazole	Antisedan
Atracurium besylate	Tracrium
Atropine sulfate	Antrocol, Di-Atro Tabs
Auranofin	Ridaura
Aurothioglucose	Solganal
Azithromycin	Zithromax
Azathioprine	Imuran
Bacitracin	ALBAC 50, (bacitracin-neomycin-polymixin)
Bacitracin methylene disalicylate	BMD 50
Baclofen	Lioresal
Barium sulfate	Barotrast
Beclomethasone dipropronate	Beclovent
Benzalkonium chloride	Zephasin
Benzocaine	Cetacaine
Betamethasone	Celestone
Bethanechol chloride	Urecholine
Bisacodyl	Dulcolax
Bismuth subcarbonate	AMFOROL
Bismuth subsalicylate	Pepto-Bismol
Bleomycin	Blenoxane
Botulism antitoxin	
Bretylium	Bretylium tosylate
Brewer's yeast	
Bromhexine*	
Bromide, potassium or sodium	
Bromocriptine mesylate	Parlodel
Bumetanide	Bumex
Bunamidine	Scolaban
Bupivacaine hydrochloride	Marcaine
Buprenorphine	Buprenex
Buspirone	Buspar
Busulfan	Myleran
Butorphanol tartrate	Torbugesic, Torbutrol
Caffeine	Cafergot
Calcitonin	Calcimar, Miacalcin
Calcium carbonate	OSTEO-FORM, Tums, Rolaids
Calcium chloride	CAL ORAL PLUS
Calcium EDTA	Versenate
Calcium gluconate 10%	Calglucon
Calcium lactate	Calphosan
Captan powder, 50%	Orthocide
Carbamazepine	Epitol
Carbenicillin	Geocillin
Carbenicillin indanyl	Geopen
Carbimazole	
Carfentanil	Wildnil
L-carnitine	Tyson
Carprofen	Rimadyl
Cefaclor	Ceclor
Cefadroxil	Cefa-Drops, Cefa-Tabs
Cefamandole	Mandol
Cefazolin sodium	Ancef, Kefzol
Cefonicid	Monocid
Cefoperazone sodium	Cefobid

Table 1. Generic and Trade Names *Continued*

Generic	Trade Name
Famotidine	Pepcid
Fenbendazole	Panacur
Fentanyl citrate	Oralet
Fentanyl/droperidol	Innovar-Vet
Fenthion	Lysoff, Spotton, Tiguvon
Ferric cyanoferrate	Prussian Blue
Ferrous sulfate	Feosol, Ferrodex
Filgrastim	Neupogen
Flavoxate	Urispas
Florfenicol	NUFLOR
Fluconazole	Diflucan
Flucytosine	Ancobon
Fludrocortisone	Florinef
Flumethasone	Flucort
Flunixin meglumine	Banamine
5-Fluorouracil	Adrucil, Efudex
Fluoxetine	Prozac
Flurazepam	Dalmane
Flurbiprofen	Ocufen
Folic acid	Feosol Plus, Vetriderma
Folinic acid	Wellcovorin
Follicle-stimulating hormone	FSH-P, PMS
Fomepizole (4-methylpyrazole)	Antizol-Vet
Furazolidone	Furox Aerosol Powder
Furosemide	Lasix
Gentamycin	Garacin, Gentocin
Gentamicin SO_4 0.1%	Garacin, Garasol
Glipizide	Glucotrol
Glucagon	Glucagon
Glucose 40% ophthalmic	Glucose-40
Glycerin	Ophthalgan, Optim
Glyceryl guaiacolate	Geocolate
Glycerol monoacetate	Glycerol monoacetate
Glycopyrrolate	Robinul
Gold sodium thiomalate	Myochrysine
Gonadotropin-releasing hormone	Cystorelin
Granulocyte colony-stimulating factor (filgrastim)	Neupogen
Griseofulvin	Fulvicin P/G, Fulvicin U/F
Guaifenesin	Amonidrin, Robitussin
Haloperidol	Haldol
Halothane	Fluothane
Heparin	Hep-Lock
Hetacillin	Hetacin-K
Hetastarch (see Hydroxyethylstarch)	Hetastarch
Hyaluronate	Hylartin, Hylalovet
Hydralazine	Apresoline
Hydrocodone bitartrate	Hycodan
Hydrocortisone	Acticort
Hydrocortisone sodium succinate	Solu-Cortef
Hydrogen peroxide 3%	Hydrogen peroxide 3%
Hydroxyethylstarch (hetastarch)	
Hydroxyurea	Hydrea
Hydroxyzine	Atarax, Vistaril
Hypertonic saline	
Ibuprofen	Advil, Motrin
Idoxuridine	Stoxil
Imidocarb dipropionate	Imizol
Imipenem; cilastatin	Primaxin
Imipramine	Tofranil
Indomethacin	Indocin
Insulin, NPH	NPH Iletin I, NPH
Insulin, PZI*	
Insulin, regular	Regular Iletin, Humulin R
Insulin, ultralente	Humulin-U
Interferon	Actimmune
Iodine	Lugol
Iohexol	Omnipaque
Iopamidol	Isovue
Ipecac syrup	Ipsatol
Ipratropium	Atrovent
Ipronidazole	
Iron dextran	
Isoflurane	AErrane, Forane
Isoniazide	Dinacrin
Isopropamide iodide	Darbid
Isopropamide/prochlorperazine	Darbazine
Isoproterenol	Isuprel
Isosorbide dinitrate	Isordil
Isotretinoin	Accutane
Isoxsuprine HCl	Vasodilan
Itraconazole	Sporanox
Ivermectin	Heartgard-30
Kanamycin	Kantrex
Kaolin; pectin	Kaopectate
Ketamine HCl	Ketaject
Ketoconazole	Nizoral
Ketoprofen	Ketofen, Orudis
Ketorolac	Toradol
Lactulose	Cephulac, Chronulac
Leucovorin	Leucovorin, Wellcovorin
Levallorphan	Levo-Dromoran
Levamisole	Ripercol, Totalon, Tramisol
Levamphetamine	
Levothyroxine (T_4)	Levothroid, Synthroid, Thyrosyn, Thyroxine-L
Lidocaine	Anestacon, Lida-Mantle, Xylocaine
Lime water	Vlemasque
Lincomycin	Lincocin
Liothyronine (T_3)	"Cytobin," Cytomel
Lisinopril	Prinivil
Lithium carbonate	Lithane, Lithotabs
Loperamide	Imodium
Lorazepam	Ativan
Luteinizing hormone	LH
Lysine-8-vasopressin	Lypressin
Mafenide 10%	Sulfamylon
Magnesium citrate	Evac-Q-Mag
Magnesium hydroxide	Gelusil-M, Milk of Magnesia, Mylanta
Magnesium sulfate	
Mannitol 20%	Osmitrol
Marbofloxacin	Zenoquin
Mebendazole	Telmintic, Vermox
Meclizine	Bonine
Meclofenamic acid	Arquel
Medetomidine HCl	Domitor, Iomitor
Medium-chain triglycerides	MCT, Portagen
Medroxyprogesterone acetate	Depo-Provera, Provera
Megestrol acetate	Megace, OVABAN
Meglumine antimonate	
Melarsomine HCl	Immiticide
Melatonin	
Melphalan	Alkeran
Meperidine HCl	Demerol
Mephenytoin	Mesantoin
6-Mercaptopurine	Purinethol
Metaproterenol sulfate	Alupent
Metaraminol bitartrate	Aramine
Methazolamide	Neptazane
Methicillin	Celbenin, Staphcillin
Methimazole	Tapazole
DL-methionine	Methio-Form, Odortrol, Pedameth, Uroeze
Methocarbamol	Robaxin
Methohexital sodium	Adria, Brevital
Methotrexate	Folex
Methoxamine HCl	Vasoxyl
Methoxyflurane	Metofane
Methylcellulose	Citrucel
Methylene blue	Urolene Blue
Methylphenidate	Ritalin

Table 1. Generic and Trade Names *Continued*

Generic	Trade Name	Generic	Trade Name
Methylprednisolone sodium succinate	Solu-Medrol	Pentobarbital	Nembutal
4-Methylpyrazole 5% solution	Antizol-Vet	Methylprednisolone	Medrol
Methylsulfonylmethane		Methylprednisolone acetate	Depo-Medrol
Methyltestosterone		Pentoxifylline	Trental
Metoclopramide	Reglan	Phenobarbital	Eskabarb, Luminal
Metoprolol	Lopressor	Phenoxybenzamine HCl	Dibenzyline
Metronidazole	Flagyl	Phentolamine	Regitine
Mezlocillin	Mezlin	Phenylbutazone	Butazolidin
Mibolerone	Cheque	Phenylephrine	Neo-Synephrine
Miconazole	Conofite, Monistat IV	Phenylpropanolamine HCl	Dexatrim, Ornade
Midazolam	Versed	Phenytoin	Dilantin
Milbemycin oxime	Interceptor	Physostigmine	Antifirium, Eserine
Milrinone	Primacor	Phytomenadione (phytonadione)	Veta-K_1
Mineral oil	Balneol	Pilocarpine 1% ophthalmic solution	
Minocycline	Minocin	Piperacillin	Pipracil
Misoprostol	Cytotec	Piperazine	Pipa-Tabs
Plicamycin (Mithramycin)	Mithracin	Piroxicam	Feldene
Mitotane (o,p-DDD)	Lysodren	Polymyxin	Aerosporin
Mitoxantrone	Novantrone	Polysulfated glycosaminoglycans	Adequan
Morphine SO_4	Asramorph P/F, Duramorph, Infumorph	Potassium chloride	Kaon-Cl, Kay Ciel
Mycobacterium cell wall fraction	Equimune I.V.	Potassium citrate	Urocit-K
Nafcillin	Nafcil, Unipen	Potassium gluconate	Tumil-K, Twin-K
Nalbuphine	Nubain	Potassium iodide	
Nalidixic acid	NegGram	Potassium permanganate (1:2000)	Potassium permanganate-$KMnO_4$
Nalmefene	Revex	Povidone-iodine	Betadine
Nalorphine HCl	Nalline	Pralidoxime chloride	
Naloxone HCl	Narcan	Praziquantel	Droncit
Naltrexone	Trexan	Prazosin	Minipress
Nandrolone decanoate	Deca-Durabolin, Decabolin	Prednisolone acetate	
Naproxen	Equiproxen, Naprosyn	Prednisolone sodium phosphate	Cortisate-20
Natamycin	Pimaricin	Prenisolone sodium succinate	Solu-Delta-Cortef
Neomycin	Biosol	Primaquine PO_4	
Neostigmine	Prostigmin, Stiglin	Primidone	Mysoline
Netilmicin		Procainamide	Pronestyl, Procanbid
Niclosamide	Nicloside	Prochlorperazine	Compazine
Nicotinamide	Niacin	Promethazine HCl	Anergan 25, Mepergan, Remsed, Phenergan
Nifurtimox	Lampit	Proparacaine	Ophthaine
Nikethamide	Coramine	*Propionibacterium acnes*	Bova-Pro, Eqstim, Immunoregulin
Nitrofurazone		Propofol	Diprivan, Rapinovet
Nitrofurantoin	Dantefur, Furadantin	Propranolol	Inderal
Nitroglycerin 2% ointment	Nitro-Bid, Nitrol	Propylthiouracil	
Nitroprusside	Nitropress, Nipride	Prostaglandin $F2_\alpha$	Lutalyse
Nizatidine	Axid	Protamine sulfate	
Norepinephrine	Levophed	Protriptyline	Vivactil
Norfloxacin	Chibroxin, Noroxin	Pseudoephedrine	Sudafed
Nystatin	Mycolog, Nilstat	Psyllium	Fiberall, Metamucil
Omeprazole	Prilosec	Pyrantel pamoate	Nemex, Strongid T
Ondansetron	Zofran	Pyridostigmine bromide	Mestinon
Orbifloxacin	Orbax	Pyrilamine maleate	Nisaval
Orgotein	Palosein	Pyrimethamine	Daraprim
Oxacillin	Bactocill, Prostaphlin	Quinacrine	Atabrine
Oxazepam	Serax	Quinidine	Duraquin
Oxtriphylline	Choledyl	Quinidine sulfate	Quinidex
Oxymetholone	Anadrol	Ranitidine HCl	Zantac
Oxymorphone	Numorphan	Rifampin	Rifamate, Rimactane
Oxytetracycline	Terramycin	Selenium	
Oxytocin	Pitocin, Syntocinon	Selegiline	Anipryl, Eldepryl
Pancreatic enzymes	Viokase	Silver sulfadiazine	Silvadene
Pancuronium bromide	Pavulon	Skin So Soft (SSS)	Skin So Soft by Avon
Paregoric (corrective mixture)		Sodium bicarbonate	Neut, Soda Mint
D-penicillamine	Cuprimine	Sodium chloride	Adsobanac, Ayr
Penicillin G aqueous (potassium or sodium)		Sodium chloride 5%	Muro 128
Penicillin G benzathine	Bicillin, Permapen	Sodium chloride 7.5%	
Penicillin G procaine	Abbocillin, Crysticillin, Depo-Penicillin, Wycillin	Sodium iodide, 20% solution	
Pentamidine isethionate	Pentam	Sodium nitrate	
Pentosan polysulfate		Sodium phosphate	Fleet Phospho-Soda
Pentazocine	Talwin	Sodium polystyrene sulfonate	Amberlite IRP-69 Resin

Table continued on following page

APPENDIX 8

Drug Dosage Tables

Table 1. Recommended Dose and Regimen*

Drug	Dose†	Route‡	Frequency§
Acarbose	100–200 mg (D)	PO	With each meal
Acemannan	2 mg	IP	Weekly
	1 mg/kg		
Acepromazine	0.025–1.13 mg/kg, max. 3 mg (D)	IM, SC, IV	
	0.56–2.25 mg/kg (D)	PO	6–8
	0.05–0.1 mg/kg, max. 1 mg (C)	IV	
	0.05–2.25 mg/kg (C)	IM, SC, IV, PO	
	0.05–1.00 mg/kg	IV, IM, SC	
Acetaminophen with codeine	10–15 mg/kg (D)	PO	8–12
	Dose based on that of codeine		
Acetazolamide	3.3–10 mg/kg (D)	PO	8
	50 mg	IV	One time
	7 mg/kg (C)	PO	8
Acetohydroxamic acid	12.5 mg/kg (D)	PO	12
Acetylcysteine	3–6 mL/hr for 30–60 min (D)	Nebulization	12
	140 mg/kg	IV	Loading dose
	70 mg/kg	PO	4–6 × 5–7 treatments
Acetylsalicylic acid[1]	5–10 mg/kg (D)	PO	24
	5–10 mg/kg (D)	PO	12–48
	6 mg/kg (C)	PO	48–72
	80 mg (C)		48
	10–25 mg/kg (D)	PO	8–12
	10–20 mg/kg (C)	PO	48
	150–300 mg/20 kg	PO	24–48 × 10 days
	Decrease dose if other anticoagulants also used		
	10 mg/kg (D)	PO	12
	6 mg/kg (C)	PO	48–72
Actinomycin D	0.015 mg/kg (D)	IV	24 × 5 days
	0.5–1.0 mg/m^2	IV	3 wk
Activated charcoal	1 g/5 mL water: give 10 mL of slurry/kg	PO	
	1–4 g/kg (granules)	PO	
	6–10 mL/kg (suspension)		
Acyclovir	200 mg	PO	6
Albendazole	25–50 mg/kg (D)	PO	12 × 5–10 days, depending on infection
	50 mg/kg (C)	PO	24 × 21 days
		PO	12 × 4 days
Albuterol	0.02–0.05 mg/kg (D)	PO	12 × 10 days
	50 μg/kg	PO	8
Aldactazide	2 mg/kg	PO	12
Allopurinol	10 mg/kg	PO	8–12 for 30 days, then every 24
Aloe vera cream	Thickness of 1/8 to 1/4 inch	Topically	6× several days then 12–24
Alpha Keri	1 capful to 1–2 quarts of water for final rinse or spray aerosol onto wet coat and rub well		
Alprazolam	0.125–0.25 mg/cat (C)	PO	12
Aluminum carbonate gel	10–30 mg/kg	PO with meals	8
Aluminum hydroxide	2–30 mL	PO	
	30–90 mg/kg	PO with meals	8–24
Aluminum magnesium hydroxide	2–10 mL	PO	2–4

Table continued on following page

Table 1. Recommended Dose and Regimen* *Continued*

Drug	Dose†	Route‡	Frequency§
Apomorphine	0.02–0.04 mg/kg (D)	IV, IM	
	0.08–0.1 mg/kg (D)	IM, SC	
	0.25 mg	Conjunctival sac	
Aprindine	1–2 mg/kg; max 100 mg (D)	PO	12
	0.1 mg/kg/min (D)	IV × 5 min	repeat q10 min as needed
Aprotinin	5000 kallikrein inhibitor units (KIU)/kg	IV, IP (preferred)	6–8
Ascorbic acid	500–1000 mg/day (D)	PO	24
	25–125 mg/kg/day (C)	PO	24
	30 mg/kg (C)	PO, SC	6 × 7 treatments
	100–500 mg (D)	PO	8–24 h
	100 mg (C)	PO	8–24 h
Asparaginase	10,000 U/m^2 (small D, C)	IV	Weekly as part of a protocol
	30,000 U/m^2 (large D)	IV	Weekly as part of a protocol
	400 U/kg (D)	IM	Once
	10,000 U (D)	IM	Once wk × 1–3 treatments
	10,000 U/m^2 (C)	IM, SC	Every 1–3 wk
Aspirin	10 mg/kg (D)	PO	12
	6–10 mg/kg (C)	PO	48–72
	25–35 mg/kg (D)	PO	8
	40–80 mg (C)	PO	48–72
	50 mg/kg (D)	PO	8–12
	0.5 mg/kg	PO	12
	25 mg/kg (C)	PO	2 times/wk
	162 mg (C)	PO	2 times/wk
	5–10 mg/kg (D)	PO	24
Astemizole	0.2 up to 1 mg/kg (D)	PO	24
Atenolol	6.25–50 mg (D)	PO	12
	0.25–1.0 mg/kg (D)	PO	24–12
	2–3 mg/kg (C)		
	5.00–12.5 mg (C)	PO	24
	2 mg/kg	PO	24
Atipamezole	Volume equivalent to medetomidine volume	IV	As needed
Atovaquone	13.3 mg/kg with fatty meal	PO	8 × 21 days
Atracurium besylate	0.1–0.25 mg/kg	IV	Initially, then 30 min later
	0.15 mg/kg	IV	
Atropine	0.022–0.044 mg/kg	IM, SC, IV	As needed
	0.04 mg/kg	PO	6–8
	0.044 mg/kg	IV	
	0.02–0.045 mg/kg	SC, IM, IV	
	0.02 mg/kg	SC	PRN
	0.2–2 mg/kg	1/4 dose IV, the rest SC, IM	
Auranofin	0.05–0.2 mg/kg (D)	PO	12; 9 mg/day max
Aurothioglucose	1st wk: 5 mg (D)	IM	
	1 mg (small D, C)	IM	
	2nd wk: 10 mg (D)	IM	
	2 mg (small D, C)	IM	Then once weekly decreasing to once monthly
	1 mg/kg (D, C)	IM, then	
Azathioprine	0.5 mg/kg (D)	PO	24–48
	2.0–2.5 mg/kg (D)	PO	24–48
	0.2–0.3 mg/kg (C)	PO	24–48
			24–48
			24
			24–48
	0.5–1.0 mg/kg	PO	24, taper to 48
	2.2 mg/kg or 50 mg/m^2 (D)	PO	24–48
			24 × 14–21 days, then 48
	2 mg/kg (D)	PO	24
Azrithromycin	5–10 mg/kg (D)	PO	12–24
	3.3 mg/kg (D)	PO	24
	10 mg/kg (D)	PO	120 (5 days)
	7–15 mg/kg (C)	PO	12–24
	5 mg/kg (C)	PO	48
Aztreonam	12–25 mg/kg	IV, IM	8–12
Baclofen	5–10 mg (D)	PO	8

Table continued on following page

Table 1. Recommended Dose and Regimen* *Continued*

Drug	Dose†	Route‡	Frequency§
Calcium EDTA	100 mg/kg/day = total dose;		5 days
	make solution of 1 g Versenate/100 mL D_5W, divide total quantity mL into 20 aliquots, 1 dose	SC	6 for 5 days
Calcium gluconate 10%	1 mL/2.5 kg	IV (slowly)	As needed
	0.5–1.5 mL/kg	IV in 5% D/W over 20–30 min	6–8 intervals
	10–15 mL	IV infusion	24
	50–150 mg/kg		
	10–15 mg/kg/hr (D)		
	150–250 mg/kg	PO (tab)	8–12
Calcium lactate	0.5–2 g (D)	PO	
	130–200 mg/kg (D)	PO	8
	0.2–0.5 g (C)	PO	
Captan powder 50%	2 tbsp/gal water	Topically, do not rinse	2–3 times/wk
Captopril	0.25–2 mg/kg (D)	PO	8–12
	2–3 mg (C)	PO	8
	3–6.25 mg (C)	PO	12
	0.5–2.0 mg/kg (D)	PO	8–12
Carbamazepine	Not recommended for dogs		
Carbenicillin	15–30 mg/kg	IV	8
	15–110 mg/kg	IV, IM, SC	6–8
Carbenicillin indanyl sodium	10–55 mg/kg	PO	8
Carbimazole	5 mg/cat	PO (induction)	8 followed by
	5 mg/cat	PO	12
Carboplatin	300 mg/m^2 (D)	IV	3–4 wk
	200 mg/m^2 (C)	IV	4 wk
Carmustine	50 mg/m^2	IV	6 wk
L-carnitine	2 g (D)	PO	8–12
	220 mg/kg (D)	IV, PO	24
	250–500 mg (C)	PO	24
Carprofen[1]	2.2 mg/kg (D)	PO	12
Cascara sagrada	1–4 mL/dog	PO	24
	0.5–1.5 mL/cat	PO	24
Castor oil	8–30 mL (D)	PO	24
	4–10 mL (C)	PO	24
Cefaclor	4–20 mg/kg	PO	8 in fasted animal
Cefadroxil	20–35 mg/kg (D)	PO	8–12
Cefamandole	6–40 mg/kg	IM, IV	6–8
Cefazolin sodium	5–25 mg/kg	IV, IM, SC	6–8
	20–25 mg/kg	IV, IM	4–8
	8–22	IV	1–2 during surgery
Cefepime	50 mg/kg	IV, IM	8
Cefixime	5–12.5 mg/kg	PO	12–24
Cefmetazole	20 mg/kg	IV	6–12
	20 mg/kg	IV	Single treatment
Cefoperazone	22 mg/kg	IV, IM	6–12
Cefotaxime	20–80 mg/kg (D)	IM, IV, SC	4–12
	20–80 mg/kg (C)	IM, IV	8
Cefotetan	30 mg/kg	IV, SC	8
Cefoxitin sodium	15–30 mg/kg (D)	SC, IM, IV	6–8
	6–40 mg/kg (D)	IV	6–8
	11–30 mg/kg (C)	IM, IV	8
	20–40 mg/kg (D)	IV	8
Cefpodoxime	5–10 mg/kg	PO	12–24
Ceftazidime	15–30 mg/kg	IV, IM, SC	6–12
Ceftiofur	2.2–4.4 mg/kg	SC	12–24
Ceftizoxime	25–50 mg/kg	IV, IM	8–12
Ceftriaxone	15–50 mg/kg	IM, IV	12
	25 mg/kg	IM, IV	Single treatment
Cefuroxime	10–30	PO, IV	8–12 with food
Cephadroxil	20–22 mg/kg (D)	PO	12
	22 mg/kg (C)	PO	24
Cephalexin	20–60 mg/kg	PO	6–12
Cephaloridine	10 mg/kg	IM, SC	8–12
Cephalothin	10–44 mg/kg	IV, IM, SC	4–8
Cephamandole	6–40 mg/kg	IM, IV	6–8
Cephapirin	10–30 mg/kg	IM, IV, SC	4–8

Table continued on following page

Table 1. Recommended Dose and Regimen* *Continued*

Drug	Dose†	Route‡	Frequency§
Cephradine	10–40 mg/kg	PO, IV, IM	6–8
Cetacaine		Topical	
Charcoal, activated	1–8 g/kg as slurry (1 g: 5 mL water) 6–12 mL/kg (suspension)	PO	As needed
Chlorambucil	0.1–0.2 mg/kg (D)	PO	24–48
	2–6 mg/m^2 (D)	PO	24–48
	20 mg/m^2 (D)	PO	7 days
	0.25–0.5 mg/kg (C)	PO	48–72
	20 mg/m^2 (C)	PO	14–21 days
	0.2 mg/kg (D)	PO	24 for 10 days, then
	0.1 mg/kg	PO	24 with prednisone
	0.1–0.2 mg/kg	PO	Once every 48 with prednisone
Chloramphenicol	25–50 mg/kg (D)	IV, PO, IM, SC	8
	50 mg (C)	PO, IV	12
Chlordiazepoxide-clidinium	1–2 tablets	PO	12
Chlorhexidine 0.5%	Apply after cleansing area		As needed
	Saturate wet dressing		12–24
Chlorothiazide	10–40 mg/kg	PO	12
	20–40 mg/kg	PO	12
Chlorpheniramine	2–8 mg/kg (D)	PO	8–12
	1–2 mg (C)	PO	8–12
	2–4 mg (C)	PO	12
Chlorpromazine	0.8–4.4 mg/kg (D)	PO	8–12 for tranquilization
	0.5 mg/kg (C)	IM, IV	6–8
	2.0–4.0 mg/kg (C)	PO	24
	0.05–0.50 mg/kg (D)	SC, IM	6–24
	1 mg/kg (D)	Rectal	8
	3.3 mg/kg (D)	PO	6–24
	1.1–6.6 mg/kg (D)	IM	6–24
	2 mg/kg (D)	PO	8–24
	0.5 mg/kg (D)	IM, IV	12 for tetanus
	2 mg/kg (D)	IM	12
Chlorpropamide	10–40 mg/kg/day (D)	PO	
Chlortetracycline hydrochloride	25 mg/kg	PO	6–8
Cholecalciferol	500–2000 U/kg/day	PO	
Cholestyramine	200–300 mg/kg	PO	As needed, 12 (D)
	1–2 g (D)	PO	12
Chorionic gonadotropin	500–1000 IU (D)	IM	Repeat in 48
	25–100 IU	IM	2/wk for 4–6 wk
	500 IU (D)	SC	Twice wk for 4 wk, then start pregnant mare serum
	500–1000 IU (D)	SC	24 for 2 days, after follicle-stimulating hormone
	250 IU (C)	IM	On days 1 and 2 of estrus
Cimetidine	5–15 mg/kg	PO, IV, IM	6–12 (D), 8–12 (C)
	5–15 mg/kg	PO, IV, SC	6
	5 mg/kg (D)	PO, IV	6–8
	10–25 mg/kg	IV, PO, IM	12
Ciprofloxacin	10–12 mg/kg	PO	12
	20–30 mg/kg	PO	12
Cisapride	0.1–0.5 mg/kg (D)	PO	8–12
	2.5–5 mg/cat	PO	8–12
Cisplatin	40–70 mg/m^2 (D)	IV	q3wk with saline solution
Clarithromycin	2.5–10 mg/kg (D)	PO	12–24
Clemastine	0.05–0.10 mg/kg (D)	PO	12
Clindamycin	5–11 mg/kg	PO	12
	22 mg/kg	PO	24
	5–10 mg/kg	IV, IM	8
	10–40 mg/kg (D)	PO, IM	8 for 2 wk for toxoplasmosis
	12.5–50 mg/kg (C)	PO, IM	12 for 2 wk for toxoplasmosis
	12.5–25 mg/kg (C)	PO, IM	12 for 2 wk for toxoplasmosis
Clofazimine	4–8 mg/kg	PO	24 for 6 wk

Table 1. Recommended Dose and Regimen* *Continued*

Drug	Dose†	Route‡	Frequency§
Cyclosporine	4–6 mg/kg	4 hr IV infusion	242 (avoid extravasation)
	5–20 mg/kg (D)	PO	24 for 5 days
	3–7 mg/kg	PO	12 (adjust dose based on monitoring)
	10 mg/kg (C)	PO	
	1–7 mg/kg (D)	PO	12 (adjust dose based on monitoring)
	1–1% solution in oil	Drop in eye	
Cyclosporine ophthalmic			
Cyclothiazide	0.5–1 mg/kg	PO	24
Cyproheptadine hydrochloride	1.1 mg/kg (D)	PO	8–12
	2–4 mg/cat	PO	12–24
Cytarabine	5–10 mg		24 for 2 wk
	30–50 mg/kg	IV, IM, SC	Once a wk
	100 mg/m^2	IV, IM, SC	24 for 4 days, then
	20 mg/m^2	Intrathecal	24 for 1–5 days
Cythioate	1.5–3.3 mg/kg	PO	Every 72 hr or 2 × wk
	0.22 mL/kg	Liquid	Every 72 hr or 2 × wk
Cytosine arabinoside	100 mg/m^2	IV	24 for 4 days
Dacarbazine	200–250 mg/m^2	IV	24 for 5 days, every 21 days
Dactinomycin	1000 mg/m^2	IV drip	Over 6–8 hr, every 21 days
	0.015 mg/kg	IV	24 for 3–5 days; wait 3 wk
	0.7–1.5 mg/m^2	IV	weekly
Danazol	5–10 mg/kg (D)	PO	12
	5 mg/kg (C)	PO	12
Dantrolene	3–15 mg (D)	PO	8–12
	1–5 mg/kg (D)	PO	8
	0.5–2 mg/kg (C)	PO	8
Dapsone	0.3–1.1 mg/kg (D)	PO	12 for 4–6 wk
	8 mg/kg (C)	PO	24 × 6 wk
	50 mg/kg (C)	PO	
	12.5–25 mg (C)	PO	12–24
	1 mg/kg (D)	PO	8 for 14 days
	1 mg/kg (D)	PO	8
	0.7–1 mg/kg	PO	8
Darbazine (plus isopropamide)	0.14–0.22 mL/kg	SC	12
	2–7 kg: 1 #1 capsule	PO	12
	7–14 kg: 1 #2 capsule	PO	12
	>14 kg: 1 #3 capsule	PO	12
Decoquinate	1/4 (1–10 lb dog) to 2 1/2 (91–100 lb dog) tsp	PO	In food, twice daily
Deferoxamine mesylate	10 mg/kg	IV, IM, SC	2 hr for 2 doses, then 8 hr for day
	10 mg/kg		
	50 mg/kg	IV	Over 5 min
Dehydrocholic acid	10–15 mg/kg	PO	8 (until urine neg. for bilirubin)
Delta-Albaplex (plus prednisolone) (plus tetracycline hydrochloride)	3–7 kg: 1–2 tab (D)	PO	24
	7–14 kg: 2–4 tab (D)	PO	24
	14–27 kg: 4–6 tab (D)	PO	24
	>27 kg: 8–8 tab (D)	PO	24
	1 tab (C)	PO	12
Demeclocycline	3–12 mg/kg	PO	6–12
Deoxycorticosterone acetate	0.5–1 mg	IM	24
	1–5 mg		
Deprenyl	See selegiline		
Dermcaps ES	1 capsule per 31.5–40 kg		
Dermcaps ES liquid	Up to 13.6 kg, give 0.5 mL		
	Up to 27.2 kg, give 1 mL		
	Up to 40.8 kg, give 1.5 mL		
Dermcaps	1 capsule per 9 kg	PO	24
Dermcaps liquid	To 4.5 kg, give 0.35 mL		
	To 9 kg, give 0.7 mL		
	To 13.6 kg give 1.05 mL		
Desmopressin acetate (DDAVP)	1 µg/kg (D)	SC, IV	90 min before surgery
	0.3 µg/kg (diluted in 50 mL saline)	IV	Infused over 15–30 min; repeat as needed
	2–4 drops	Subconjunctivally	12–24
	0.1 mg	PO	12–24
		Topically	
	1–2 drops	Intranasal, subconjunctival	12–24

Table 1. Recommended Dose and Regimen* *Continued*

Drug	Dose†	Route‡	Frequency§
Desoxycorticosterone acetate (DOCA)	0.2–0.4 mg/kg	IM	24, max. 5 mg
Desoxycorticosterone pivalate	25 mg	IM = 1 mg/day	DOCA released for 25 days
	125-mg pellet	SC = 0.5 mg/day	DOCA released for 6 months
	1–3 mg/kg (D)	IM	25–28 days
Dexamethasone	2 mg/kg	IV	then, for CNS trauma
	1 mg/kg	IV, SC	8–12, then
	0.1 mg/kg	IV, SC	8–12
	0.25 mg/kg	IV, PO, IM	6–8 for hydrocephalus
	4–6 mg/kg	IV (slowly)	for shock
	0.25–0.3 mg/kg (D)	SC, IV	Once, then
	0.25–1.25 mg/kg	PO	12–24
	0.10–0.15 mg/kg	SC, PO	12 for 5–7 days, then taper dose with immunocorticoids
	0.1–0.5 mg/kg	SC, IV	Then
	1 mg/kg	IV	8–24
	0.25–1.0 mg/cat	PO	
Dexamethasone $NaPO_4$	4–6 mg/kg	IV	
Dexpanthenol	11 mg/kg	IM	4–6
Dexrazoxane	25 mg/kg (Ratio of 10–20:1 dexrazoxane:doxorubicin)	IV	15 min before doxorubicin
Dextran 40	10–20 mL/kg	IV	24
	2 mL/kg	IV	24 in 5% D/W
Dextran 70	20–40 mL/kg	IV	24 in 5% D/W
	10–20 mL/kg	IV	24 to effect
Dextroamphetamine	5–10 mg	PO	8 with imipramine
	0.2–1.3 mg/kg	PO	As needed
Dextromethorphan	0.5–2 mg/kg (D)	PO, SC, IV	6–8
Dextrose, 50%	2 mL/kg	PO	
	0.25–1.00 mL/kg	IV	
Dextrose, 5%	40–50 mL/kg	IV, SC, IP	As needed
Dicloxacillin	5–10	PO	24
Diazepam	0.2–0.6 mg/kg (D)	IV	
	0.25 mg	PO	8
	0.5–2.2 mg/kg	PO	As needed
	0.15–0.70 mg/kg (C) or	PO	8
	2–5 mg/cat	PO	8
	1–4 mg/kg (D)	PO	6–8
	2–5 mg/kg	PO, IV	8
	1–2 mg/kg	Rectal	As needed for seizures
	0.5–1.0 mg/kg	IV	In increments of 5–20 mg
	2–5 mg/kg	IV	As needed for seizures
	0.25 mg/kg (D)	PO	6–8
	0.1–0.2 mg/kg (D)	IV slowly	As preanesthetic for Scotty cramps
	0.22–0.44 mg/kg (<5 mg)	IV, IM	
	0.5 mg/kg	IV	
	0.15 mg/kg (D)	PO	8
	2.5–5.0 mg (C)	PO	6–8 for reflex dyssynergia
	0.5 mg/kg	IV	
	1.25–2.5 mg/cat	PO	8–12
	0.05–0.4 mg/kg (C)	IV, PO, IM	24 or 48
	1 mg (C)	PO	24 as appetite stimulant
	2–10 mg	PO	8 for urethral obstruction
	1–2 mg (C)	PO	12
	0.5–2.2 mg/kg (D)	PO	As needed for separation anxiety
Diazoxide	5–13 mg/kg (D), max. 40 mg/kg	PO	Divided 8–12
Dichlorphenamide	2–5 mg/kg (D)	PO	8–12
	1 mg/kg (C)	PO	8–12
Dichlorvos	11–22 mg/kg	PO	Repeat in 3 wk
	26.4–33 mg/kg (D)	PO	
	11 mg/kg (puppies)	PO	
	11 mg/kg (C)	PO	

Table continued on following page

Table 1. Recommended Dose and Regimen* *Continued*

Drug	Dose†	Route‡	Frequency§
Dipyridamole	4–10 mg/kg	PO	24
Dipyrone	25–100 mg/kg (D)	IM, IV, SC, PO	8
	25 mg/kg (C)		8 (low dose); 12–24 (high dose)
Disodium EDTA	0.37% solution		Lavage cornea for 15–20 min
	1% solution 1–2 drops	Topically	12 for several wk
Disophenol	10 mg/kg (0.22 mL/kg) (D)	SC	Repeat in 2–3 wk
	7.7 mg/kg (D)	SC	Repeat in 7 days
Disopyramide PO_4	6–15 mg/kg (D)	PO	8
	>18 kg: 100 mg (D)	PO	6–8
Dithiazanine iodide	6.6–11 mg/kg	PO	24 for 7–10 days
Divalproex sodium	See Valproic acid		
DL-Methionine	See Methionine		
Dobutamine HCl	5–40 µg/kg (D)	IV infusion	1 min
	2.5–15 µg/kg (C)	IV infusion (caution)	1 min
Docusate calcium, sodium	25–200 mg (D)	PO	12
	50 mg (C)	PO	12–24
Domperidone	2 mg/kg	PO	12–24
	250 mg/12 mL glycerin	Rectal	1 (repeat × 1)
	2–5 mg/dog or cat	PO	
	0.1–0.3 mg/kg	IM, IV	12
Dopamine HCl	2–25 µg/kg (up to 50 µg/kg if severe hypotension or shock)	IV infusion	1 min
	2–5 µg/kg (low dose)	IV infusion in 5% D/W	1 min
	2–10 µg/kg	IV infusion 40 mg in 500 mL	1 min
Doxapram	1–5 mg/kg	IV	As needed
	1–2 drops	Sublingual	
	0.1 mL or 10 mg/m^2	IV (umbilical vein)	
Doxepin HCl	3–5 mg/kg (max. 150 mg) (D)	PO	12
	0.5–1.0 mg/kg (D)	PO	12
Doxorubicin	30 mg/m^2 or 10 mg/m^2	IV	21 days or 7 days
	250 mg/m^2 (D); max. cumulative		
	20–30 mg/m^2 (C)	IV	21–28 days
Doxycycline HCl	5–10 mg/kg	PO, IV	12–24
Doxylamine succinate	1.1–2.2 mg/kg	PO, SC, IM	8–12
	12 for 2–4 wk		
Edetate calcium disodium	25 mg/kg (up to 100 mg/kg in dogs) of 1% solution (2 g max)	SC	Every 6 hr for 5 days
Edrophonium Cl	0.11–0.22 mg/kg (D)	IV	Maximum of 5 mg
	0.1–0.5 mg (puppies)	IV	
	2.5 mg/cat	IV	
Emetine	1–2.5 mL/kg, up to 6.6 mL/kg (D)	PO	
	3.3 mL/kg, dilute 50:50 with water (C)	PO	
Endotoxin antisera	4–8 mg/kg	IV	Once
Enalapril	0.2–1.0 mg/kg (D)	PO	12–24
	0.25–0.50 mg/kg (C)	PO	12–24
Enflurane	Induction: 2%–3%		
	Maintenance: 1.5%–3.0%		
Enilconazole	5% solution	Topically	12 for 7–10 days
	10–20 mg/kg (10% solution; 50:50 water)	Instill into nasal sinus	12 for 10–14 days
	Dilute to 0.2% solution	Wash	72–96
Enrofloxacin	5.0–20.0 mg/kg (D)	PO, SC, IM, IV	12–24
	2.5–5.0 mg/kg (C)	PO, SC, IM, IV	12
	5–15 mg/kg	PO	12
Ephedrine	2–5 mg (C)	PO	8–12
	1–2 mg/kg (D)	PO	8–12
	4 mg/kg or 12.5–50 mg/dog	PO	8–12
	2–4 mg/kg (C)	PO	8–12
	1/4 to 1/2 tablet (D)	PO	4–6
	1/4 tablet (C)	PO	4–6
	Use 1:10,000 (0.1 mg/mL)		

Table continued on following page

Table 1. Recommended Dose and Regimen* *Continued*

Drug	Dose†	Route‡	Frequency§
Foscarnet sodium (phosphonoformate)	20–30 mg/kg (D)	IV, PO	8
	13.3 mg/kg (C)	IV, PO	8
Furazolidone	4 mg/kg (C)	PO	12 for 7–10 days
	2.2 mg/kg	PO	8 for 7–10 days
	8–20 mg/kg	PO	8 for 7 days
Furosemide	2–4 mg/kg (up to 8 mg/kg for acute renal failure)	IV, IM, PO	8–12 or as needed, adjust to lowest dose possible
	0.5–2.0 mg/kg	PO	12
	1–2 mg/kg	PO	12
	1–2 mg/kg	PO, SC	12–24
	5 mg/kg	IV, IM, SC, PO	8–12 or each hr IV infusion
	2–5 mg/kg	IV	As needed
Gabapentin	300–1200 mg (D)	PO	8
Gamma globulin	1 g/kg	IV	6–12
Gemfibrozil	150–300 mg/g (D)	PO	12
Gentamicin[∥]	4–8 mg/kg (D)	IV, IM, SC	12–24
Gentamicin SO_4 0.1%	Apply light coating	Topically	12–24
Glipizide	0.25–0.5 mg/g (C)	PO	8–12
	2.5–7.5 mg/g (C)	PO	8–12 (gradual increase to maximum dose as needed based on serum glucose)
Glucagon	0.03 mg/kg (D)	IV, IM	
Glucose-40	Apply 1/8 inch	Topically	2–6 times daily
Glyburide	0.2 mg/kg	PO	Daily
Glycerin	1–2 mL/kg of 50% solution	PO	Repeat once at 8 hr
Glyceryl guaiacolate	110 mg/kg	IV	As needed
Glyceryl monoacetate	0.55 mg/kg hourly to 2–4 mg/kg	IM	
Glycopyrrolate	0.005–0.010 mg/kg	IV, IM	As needed
	0.01–0.02 mg/kg	SC	8–12
	0.01–0.02 mg/kg	SC, IM	As needed
Gold sodium thiomalate	1–5 mg	IM	1st wk
	2–10 mg	IM	2nd wk
	1 mg/kg	IM	Maintenance: once/week
	125–250 ng/kg		
Gonadotropin-releasing hormone	50–100 μg	IM	For 1–3 treatments
	50 μg (D)	IV	
	25 μg (C)	IM	After mating or on day 2 of estrus
	50–100 μg (D)	SC, IV	If no response, repeat in 4–6 days
Gonadotropin, chorionic	22 U/kg (D)	IM	24–48 or
	44 U (D)	IM	Once
Granulocyte colony-stimulating factor (hematopoietic growth factor, filgrastim, granisetron)	3–10 μg/kg (C)	SC	12
	3–10 μg/kg (C)	SC	24
	10–100 μg/kg (D)	SC	24
Griseofulvin	10–30 mg/kg	PO	24 (or divide 8–12)
	50 mg/kg	PO	24 (or divided 8–12)
	80–130 mg/kg	PO	24 (or divided 8–12)
	25 mg/kg	PO	24 (or divided 8–12)
	5–10 mg/kg	PO	24
	20–50 mg/kg	PO	24
Growth hormone	0.1 IU/kg (D)	SC	48 for 30 days
	0.1 IU/kg (D)	SC	24 for 3 days/wk for 4–6 wk
Guaifenesin	44–88 mg/kg	IV	
	33–88 mg/kg	IV	
	110 mg/kg (D)	IV	
Halothane	Induction: 3% Maintenance: 0.5–1.5%		
Hemoglobin (polymerized bovine)	10–30 mL/kg	IV	Once

Table 1. Recommended Dose and Regimen* *Continued*

Drug	Dose†	Route‡	Frequency§
Idoxuridine	0.1% solution: 1 drop (C)	Apply topically	3–6 times daily
		Topically	1
	0.5% ointment (C)	Topically	2
Imidocarb dipropionate	5–7.5 mg/kg (D)	IM, SC	14–21
Imipenem-cilastin	2–10 mg/kg	IM or slow IV infusion	6–8
	2.0–5.0 mg/kg (C)	IV	8
Imipramine	0.5–1.0 mg/kg (D)	PO	8
	5–15 mg (D)	PO	12
	2.5–5.0 mg (C)	PO	12
	2.2–4.4 mg/kg (D)	PO	12–24
Insulin, neutral protamine Hagedorn (NPH)	<15 kg: 1 U/kg (D)	SC	12–24
	>25 kg: 0.25–0.50 U/kg (D)	SC	12–24
	0.25–0.5 U/kg/day (C)	SC	12–24
	1–3 U (C)	SC	12–24
	3–5 U (C)	SC	24 to effect
Insulin, protamine zinc insulin (PZI)	0.5–1 U/kg	SC	12–24
	1–3 U (C)	SC	12–24
Insulin, regular	1 U/100 mL IV fluid, 0.025–0.05 U/kg/hr		
	<3 kg: 1 U/animal initially, then 1 U/animal	IM	1
	3–10 kg: 2 U/animal initially, then 1 U/animal	IM	1
	>10 kg: 0.25 U/kg initially, then 0.1 U/kg	IM	1
	0.2 U/kg, then 0.1 U/kg		Hourly until glucose <250 mg/dL
	2–5 U (C)	SC	6, to effect
	0.5 U/kg (D)	SC	3–8
	0.25 U/kg (C)	SC	3–8
Insulin, Ultralente	Dog <15 kg: 1 U/kg	SC	24 to effect
	Dog >25 kg: 0.5 U/kg	SC	24 to effect
	0.25–0.5 U/kg (C)	SC	24
	1–3 U (C)	SC	12–24
Interferon-α_2 (human recombinant)	15–30 U/cat	IM, SC, PO	24 on alternate weeks
	0.5–5.0 U/kg (C)	PO	24
	1 U/cat	PO	24
	15–30 U/cat	PO, IM, SC	24 on alternate weeks
	10 U	PO	24
	0.22 U/kg (D)	PO	24
	Add 3 million I to 1 L sterile solution; divide stock solution into aliquots and freeze; thaw and dilute when needed to produce 30 U/mL dispensing solution		
Iodine	50–100 mg/cat	PO	24
Iodide sodium, potassium 20% solution	20 mg/kg (C)	PO	12–24
	40 mg/kg (D)	IV, PO	8–12
Iohexol			
Iopamidol	0.25 mL/kg	Intrathecal	
Ipecac syrup	1–2 mL/kg, up to 15 mL (D)	PO	Repeat for 1 in 20 min
	3.3 mL/kg (dilute 1:1 with water) (D)	PO	
Ipodate	15 mg/kg	PO	12
Ipronidazole	126 mg/L water (D)	PO	Ad libitum for 7 days
Iron dextran	10–20 mg/kg followed by oral ferrous sulfate (D)	IM	Once
	50 mg (C)	IM	At 18 days of age
Isoflurane	Induction: 5%		
	Maintenance: 1.5–2.5%		
Isometheptene	0.5–1.0 mL (D)	IM	8–12
	1 tablet (D)	PO	12
	0.25–0.50 mL (C)	IM	12
	0.5 tablet (C)	PO	12
Isoniazid	10–20 mg/kg	PO	24

Table 1. Recommended Dose and Regimen* *Continued*

Drug	Dose†	Route‡	Frequency§
Ketoprofen	1.1 mg/kg (D)	IV, PO	24 up to 5 days
	0.5 mg/kg (C)	PO	24
Ketorolac tromethamine	0.5 mg/kg (D)	PO, IM, IV	12 × 2 doses
L-Asparaginase			
Lactated Ringer's solution	40–50 mL/kg/day	IV	
	90 mL/kg (D)	IV	
	60 mL/kg (C)	IV	
Lactoferrin	40 mg/kg (C)	Topical	24
Lactitol	250 mg	PO	12
Lactulose	0.5 mL/kg (D)	PO	8 or 2–3 soft stools/day
	5–45 mL/dog	PO	8
	2.5–5.0 mL/cat	PO	12–24
	0.25–1.0 mL/cat	Rectal	
	5–10 mL diluted 1:3 with water (C)		
	1 mL/4.5 kg (D)	PO	8 (to effect)
Lenperone	0.22–0.88 mg/kg (C)		
Leucovorin	3 mg/m^2 (D)	IM, PO, IV	Within 3 hr of methotrexate
		PO	
Levallorphan	0.02–0.20 mg/kg	IV	As needed
Levamisole	10–11 mg/kg (D)	PO	24 for 6–12 days for microfilaricide
	10 mg/kg (C)	PO	24 for 7 days
	2–5 mg/kg (D)	PO	48 for immune stimulation
	0.5–2.0 mg/kg (D)	PO	3× weekly
	7.5 mg/kg (D)	PO	24
	25 mg/kg (C)	PO	48 for 10–14 days for lung worms
	25 mg (C)	PO	48 for 3 treatments
	5–8 mg/kg (D)	PO	Once
	Up to 10 mg/kg	PO	For 2 days for hookworms
	20–40 mg/kg (C)	PO	48 for 5–6 treatments
	4.4 mg/kg (C)	PO	Once as immune stimulant
Levarterenol	2–4 mg/500 mL	IV	Infuse to effect
Levo-amphetamine	1–4 mg/kg (D)	PO	As needed
Levodopa	6.8 mg/kg initially, then 1.4 mg/kg		6
Levothyroxine (T_4)	22 μg/kg (D)	PO	12–24
	20–32 μg/kg (D)	PO	24
	0.5 mg/m^2 (D)	PO	24
	10–30 μg/kg (C)	PO	Divide every 12 hours
	50–100 mg/kg (C)	PO	24
Lidocaine	2–4 mg/kg (D)	IV bolus, then	
	25–75 μg/kg	IV infusion	Min
	8 mg/kg over 10 min (D)	IM	1.5
	0.25–1.00 mg/kg (C)	IV bolus, then	
	10–40 μg/kg	IV infusion	Min
Lime sulfur	1:20 dilution (D)		
	1:40 dilution	Dip, air-dry	Repeat weekly for 6 wk
Lime water	5 mL/kg	PO	
Lincomycin	11–33 mg/kg	PO, IV, IM	12–24
Liothyronine, T_3	4–6 μg/kg (D)	PO	8
	4.4 μg/kg	PO	8–12
Lisinopril	0.25–0.50 mg/kg	PO	24
Lithium carbonate	21–26 mg/kg (D)	PO	24
	10 mg/kg (D)	PO	12
Lobaplatin	35 mg/m^2	IV	3
Lomustine	60 mg/m^2 (D) up to 80 mg/m^2	PO	5–8 wk
Loperamide	0.08–0.20 mg/kg (D)	PO	8–12
	0.1–0.3 mg/kg (C)	PO	12–24
	0.08–1.16 mg/kg (C)	PO	12
Lufenuron	5 mg/kg (D)	PO	24 with meal
	15 mg/kg (C)	PO	24 with meal
Lufeneron/milbemycin	1 tablet per appropriate-sized dog	PO	
Luteinizing hormone (LH)	50 IU (C)	IM	After mating
Lysine-8-vasopressin	1–2 sprays	Subconjunctival	8–24

Table 1. Recommended Dose and Regimen* *Continued*

Drug	Dose†	Route‡	Frequency§
Mafenide 10%	Apply to thickness of 1/4 to 1/2 inch, wash off	Topical	12 24
Magnesium citrate	2–4 mL/kg	PO	
Magnesium hydroxide	5–30 mL (D)	PO	12–24
	5–10 mL (C)	PO	8–24
	15–50 mL/per dog	PO	
	2–6 mL/cat	PO	24
	3–5 × the above dosages		
Magnesium oxide	1–2 mEq/kg	PO	24
Magnesium salts	0.75–1 mEq Mg^{2+}/kg	IV	Over 24 hr, constant rate infusion; thereafter, over 1–2 hr (repeat every 4–6 hr if necessary)
	0.3–0.5 mEq/kg/day		
Magnesium sulfate (25%)	5–15 mL	IM, IV	
Mannitol 20%	0.25–0.5 g/kg of 15–25% solution	IV over 15–60 min IV over 15–20 min	
	1–3 mg/kg		
	1.5 mg/kg	IV	Once
	1 g/kg of 5–25% solution	IV to maintain urine flow	
Marbofloxacin	2.5–5 mg/kg (D)	PO	12
Mebendazole	22 mg/kg with food		24 for 3 days
Mechlorethamine HCl	5 mg/m^2 (D)	IV, IT	As needed
Meclizine	12.5 mg (C)	PO	24, 1 hr before riding
	25 mg (D)	PO	24, 1 hr before riding
Meclofenamic acid	1/4 tsp granules/5 kg (D)	PO	24
	1–1.1 mg/kg/day (D)	PO	24 for 5–7 days
Medetomidine HCl	0.01–0.08 mL/kg	IV, IM	
Medium-chain triglycerides	1 oz/10 kg with each meal	PO	dd 6–8
	0.5–1.0 oz/10 kg (max 1 tbsp per meal) or 1.0–2.2 mL/kg/day with food (D)	PO PO	
Medroxyprogesterone acetate	1–2 mg/kg (C)	IM	Once weekly; stop 7–10 days before
	10 mg/kg (D)	IM, SC	As needed
	10–20 mg/kg (C)	SC	As needed up to three injections per year
	20 mg/kg once (D)	IM	Repeat in 3–6 months if needed
	50–100 mg once (C)	SC, IM	Repeat in 3–6 months if needed
	100 mg (C)	IM	Then
	30–50 mg		30 days
	50 mg (C)	IM	Then
	15–25 mg		30 days
Megestrol acetate	2.5–5.0 mg (C)	PO	24 for 10 days, then 48 for 5 treatments, then as needed for gingivitis
	2.5–5.0 mg (C)	PO	24–48 for 14–21 days until remission, then 1–2 wk
	Proestrus: 2.2 mg/kg/day (D)	PO	For 8 days
	Anestrus: 0.55 mg/kg/day (D)	PO PO	For 32 days
	5 mg/cat for 3 days, then 2.5–5.0 mg once/wk for 10 wk		
	2.5–5.0 mg (C)	PO PO	24 for 10 days, then 48 for 7–14 days for endocrine alopecia
	5–10 mg (C)	PO	48 for 10–14 treatments, then every 2nd wk for eosinophilic ulcers
	2.5–5.0 mg	PO	7 days to prevent estrus
	5 mg	PO	24 for 5 days
	25 mg	IM	6 months
	1.1–2.2 mg/kg (D)	PO	24 as needed for behavioral disorders
	2–4 mg/kg (C)	PO	
	Reduce to 1/2 dose at 8 days (C)		Once daily
	2.5–5.0 mg (C)	PO	24 for 5–10 days, then once weekly

Table continued on following page

Table 1. Recommended Dose and Regimen* *Continued*

Drug	Dose†	Route‡	Frequency§
Megestrol acetate *Continued*	5 mg (C)	PO	24 for 5 days, then twice weekly for 8 days for skin problems
	5 mg/cat		24 for 4 months, then weekly for 4 for asthma
	5.0 mg/cat	PO	24 for 3 days, then weekly for 10 for chemical contraception
	2.5 mg/cat	PO	
	2.5 mg/cat	PO	24 for 8 wk
			weekly for 18 months
Meglumine antimonate	100 mg/kg (D)	IV, SC	24 for 3–4 wk, with allopurinol
	200 mg/kg (D)	IV, SC	48, with allopurinol
	5–30 mL	IV, IM, IP	48–72
Melarsomine dihydrochloride	Two 2.5 mg/kg doses (D)	IM	24 hr apart, repeat in 4 months
Melatonin	1–2 mg (D)	SC	24 for 3–5 days
Meloxicam	0.2 mg/kg (D)	PO	Loading dose followed by 0.1 mg/kg every 24 hours
	0.1 mg/kg	PO	
Melphalan	0.1 mg/kg (D)	PO	24 for 10 days, then
	0.5 mg/kg	PO	24 for 2 wk, then
	0.5 mg/kg	PO	48
	2–4 mg/m^2 (D)	PO	24–48
	1.5 mg/m^2 (D)	PO	Daily for 7–10 days
	0.5–0.10 mg/kg (D)	PO	Daily for 10 days, then 48 hr
	2 mg/m^2 (C)	PO	48
Menadiol			
Meperidine HCl	3–10 mg/kg (D)	IM	As needed
	5–10 mg/kg (D)	IV, IM	As needed
	1–5 mg/kg (C)	IM	As needed
	2.5–6.5 mg/kg (D)	IM	
	2.2–4.4 mg/kg (C)	IM	
Mephenytoin	10 mg/kg (D)	PO	8
Mepivacaine	Local infiltration as needed	Local	Every 30 sec until reflexes absent
	0.5 ml (1–5 mL) of 2%	Epidural	
2-Mercaptopropionyl glycine	30–40 mg/kg/day (D)	PO	
6-Mercaptopurine	50 mg/m^2 or	PO	24
	2 mg/kg	PO	24, in a protocol
Meropenem	20 mg/kg	IV	8
	40 mg/kg	IV	8
Mesalamine	10–20 mg/kg (D)	PO	6–8
Mesna	40% of cyclophosphamide dose × 6 at time of cyclophosphamide treatment; follow with repeat dose (24-hr infusion)	PO, IV, SC, IM	3
Metamucil	2–10 g (D)	In moistened food	12–24
	2–4 g (C)	In moistened food	12–24
Metaproterenol sulfate	0.325–0.65 mg/kg	PO	4-6
Metaraminol	0.01–0.10 mg/kg or 10 mg in 250 mL 5% D/W	IV slowly IV	To effect
Metformin	2 mg/kg (C) (follow-up studies needed)	PO	12
Methazolamide	1–2 mg/kg (D)	PO	8
	1–2 mg/kg (C)	PO	12
	2–4 mg/kg (max dose 4–6 mg/kg)	PO	8–12
Methenamine hippurate	500 mg/dog	PO	12
	250 mg/cat	PO	12
Methenamine mandelate	10–20 mg kg (D)	PO	12
		PO	6–12
Methicillin	20 mg/kg	IM, IV	6
Methimazole	5 mg/cat (induction)	PO	8–12, followed by 8–12
	2.5–5.0 mg/cat	PO	
	40 mg/17 kg (D)		
DL-Methionine	0.2–1 g (D)	PO	8
	0.2–1.5 g (adult cats only)	PO, added to food	24

Table 1. Recommended Dose and Regimen* *Continued*

Drug	Dose†	Route‡	Frequency§
Methocarbamol	Initial: 44–66 mg/kg (D)	PO	8–12
	20–66 mg/kg	PO	8–12; discontinue after 5 days of no response
	44 mg/kg	IV	
	55–220 mg/kg; give 1/2 dose rapidly until relaxation occurs and continue (not to exceed 330 mg/kg/day)	IV	For strychnine or tetanus poisoning
	Initial: 44–66 mg/kg (D)	PO	
Methohexital	2.5% solution: 11 mg/kg	IV	
Methotrexate Na	2.5 mg/m^2 or 0.3–0.5 mg/m^2	PO	24 or 2–3× weekly
		IV	Weekly, in a protocol
	2.5 mg/m^2 (D)	PO	24
	5 mg/m^2 (D)		On days 1 and 5 of a weekly maint.
	0.3–0.8 mg/kg (C)	IV	On day 14 with 5 mg prednisone PO 12 hr
	2.5–5.0 mg/m^2	PO	24
	10–15 mg/m^2 (C)	"High dose"	1–3 wk
	5–10 mg/m^2 (D)	PO, IV, IM	
Methoxamine HCl	0.1–0.8 mg/kg (D)	IV slowly	
	200–250 µg/kg or	IM	
	40–80 µg/kg	IV	
Methoxyflurane	Induction: 3%		
	Maintenance: 0.5%–1.5%		
Methscopolamine bromide	0.3–1.0 mg/kg (use cautiously in cats)	PO	8
Methylcellulose	0.5–5.0 g (D)	PO	
	1.0–1.5 g (C)		
Methylene blue	8.8 mg/kg (1% solution)	IV, slowly	Repeat as needed
	3 mg/250 mL 0.9% NaCl	IV over 30–40 min	Staining maximal at 25 min
	100–300 mg	PO	Daily
	1 mg/kg	IV, slowly	
Methylphenidate	5–10 mg (D)	PO	8–12
	2–4 mg/kg (D)	PO	As needed
Methylprednisolone	0.5–1.0 mg/kg	PO	12
Methylprednisolone acetate			2 wk for 2–6 treatment
	10–40 mg (C)	SC, IM, intralesional	
	4–12 mg (D)	Subconjunctivally	7 days
	1–23 mg/kg (C)	IM	
	1 mg/kg (D)	IM	1–3 wk
	5.5 mg/kg (C)	SC, IM	1–24 wk
Methylprednisolone sodium succinate	30 mg/kg (D)	IV	Loading, then
	15 mg/kg	IV	2 hr later, then
	10 mg/kg	IV, SC	6 for 2 days, then taper dose over 5–7 days
	30–35 mg/kg (D)	IV	Once
4-Methylpyrazole, 5% solution	20 mg/kg (D)	IV	Loading, then
	15 mg/kg (D)	IV	At 12 and 24 hr, then
	5 mg/kg (D)	IV	At 36 hr
Methyltestosterone	1–2 mg/kg (D); max. 25 mg/day	PO	24 for 5–7 days
		PO	24
	1–2 mg/kg; max. 30 mg/day		
	0.5–1.0 mg/kg (D); max. 30 mg/day	PO	48
		PO	24–48
	5–25 mg/dog	PO	48
	1–2.5 mg/cat		
Metoclopramide	0.2–0.5 mg/kg	PO, SC, IM	8
	0.01–0.02 mg/kg/hr (D)	IV infusion	
	1.0–2.0 mg/kg	IV infusion	24 hr
	0.2–0.4 mg/kg	PO	8, 30 min before meals and at bedtime
	0.3 mg/kg (C)	PO	
Metoprolol	5–50 mg/dog	PO	8
	0.5–1.0 mg/kg (D)	PO	8
	2–15 mg/cat	PO	8
	12.5–25.0 mg (C)	PO	12

Table continued on following page

Table 1. Recommended Dose and Regimen* *Continued*

Drug	Dose†	Route‡	Frequency§
Moxidectin	3 μg/kg (D)	PO	
	25–300 μg/kg (D)	PO	
Mycobacterial cell wall extract	1.5 mL	IV, deep IM	24 × 1 day of treatment
Nadolol	0.25–0.50 mg/kg	PO	12
Nafcillin	10 mg/kg	PO, IM	6
Nalbuphine HCl	0.75–1.50 mg/kg	IV	
	0.03–0.10 mg/kg (D)	IV	
Nalmefene (not licensed in USA)	1–4 mg/kg (D)	SC	
Nalorphine HCl	0.1 mg/kg (D) (max. 5 mg)	IV	1 mg for every 10 mg of morphine
	0.1 mg/kg (C) (max. 1 mg)	IV	
	0.44 mg/kg	IV, IM, SC	
Naloxone HCl	20 mg	SC	
	2 mg/kg	IV infusion	1
	0.01–0.04 mg/kg	IV	To effect, repeat as needed
	0.04 mg/kg (D)	IM, IV, SC	
	0.05–0.1 mg/kg (C)	IV	
Naltrexone (Trexan)	0.01 mg/kg	SC	
	1 mg/kg (D)	SC	
	2.2 mg/kg	PO	12–24
Nandrolone decanoate	1.0–1.5 mg/kg (D)	IM	Weekly
	5 mg/kg (D) (max. 200 mg/wk)	IM	2–3 wk
	1–3 mg/kg (D) (max. 200 mg)	IM	Weekly
	10–50 mg (C)	IM	Weekly
Naproxen	1.1–2.2 mg/kg (D)	PO	24–48
Natamycin		Topically	3–8
N-acetylcysteine			
Neo-Darbazine	4.5–9.0 kg: one #1 capsule	PO	12
	9.0–13.6 kg: two #1 capsules	PO	12
	13.6–27.3 kg: three #1 capsules	PO	12
	13.6–27.3 kg: one #3 capsule	PO	12
Neomycin	10–20 mg/kg (D)	PO	8–12
	7 mg/kg	IM, IV, SC	24 (nephrotoxic)
	10–20 mg/kg	Rectal (dilute in water)	6
Neostigmine	1–2 mg (D)	IM	As needed
	5–15 mg (D)	PO	As needed
	0.05 mg/kg (D)	IM	
	Less than 5 kg = 0.25 mg (D)	IM	6
	5–25 kg = 0.25–0.5 mg (D)	IM	6
	>25 kg = 0.5–0.75 mg (D)	IM	6
	1–40 μg/kg (D)	IM, SC	Administer with 0.04 mg/kg atropine IV
	40 μg/kg (D)	IM	
	20 μg/kg	IV	
Nicotinamide	500–1000 mg	IM	Once, then
	200–300 mg	IM	4, then
	200 mg	PO	24 for 2 wk
Niclosamide'	157 mg/kg (D)	PO	Once
Nifedipine	Dosage not established		
Nifurtimox (not available in the United States)	2–2.5 mg/kg (D)	PO	4 for 3 months
	8 mg/kg	PO	24
Nikethamide	7.8–31.2 mg/kg	IV, IM, SC	
Nitrofurantoin	4 mg/kg	PO	6–8
	4 mg/kg	PO	24
Nitroglycerin 2% ointment	5–30 mm (D)	SC	4–12
	1/4–2 inch (D)	SC	6–8
	4–12 mg (D) (max. 15 mg)	Topically	6–8
	1/8 to 1/4 inch (C)	SC	6–8
Nitroprusside	0.5–10 μg/kg (3 μg/kg)	IV infusion	1 min (use 50 μg/mL dilution)
Nitroscanate	50 mg/kg (D)		
Nizatidine	5 mg/kg (D)	PO	24
Norepinephrine bitartrate	0.05–0.30 μg/kg	IV	1 min

Table continued on following page

Table 1. Recommended Dose and Regimen* *Continued*

Drug	Dose†	Route‡	Frequency§
Paclitaxel	5 mg/kg (C)	IV	Pretreat for anaphylactoid reaction
Pancreatic enzyme	1 tablet		In food (crush pills)
	1–2 tsp		In food
	0.5–1.0 tsp	PO	In food
	2 tsp/20 kg body weight		
	1–3 tsp/0.45 kg of food		In food 20 min before feeding
Pancreatin	2–10 tablets (D)		In food
	1–2 tablets (C)		In food
Pancuronium bromide	0.1 mg/kg (D)	IV	
	0.03 mg/kg (D)	IV	
	0.06–1.00 mg/kg (D)	IV	
		With methoxyflurane	
		With halothane	
	0.044 mg/kg	IV	Then
	0.11 mg/kg	IV	
Paregoric	0.05–0.06 mg/kg	PO	8–12
	(5 mL of paregoric corresponds to approx 2 mg of morphine)		
Paromomycin (aminosidine)	125–165 mg/kg	PO	12 × 5 days
Paroxetine	1/8 to 1/4 of 10-mg tablet	PO	24
Parvaquone	10–30 mg/kg	IM	24
D-Penicillamine	10–15 mg/kg	PO	12
	125 mg divided	PO	24, then 12
	125–250 mg	PO	Before feeding
	15 mg/kg (D)	PO	12 with food
	33–100 mg/kg/day (D)	PO	Divided every 4 hr for 7 days, wait 7 days and repeat
Penicillin G, aqueous (K or Na)	20,000–55,000 U/kg	IV	4–6
	22,000 U/kg	IV	6
	20,000–55,000 U/kg	IM, IV, SC	4
	40,000 U/kg	PO	6 on empty stomach
	20,000–55,000 U/kg	IM, IV, SC	4
Penicillin G benzathine	50,000 U/kg	IM	5 days
Penicillin G procaine	20,000–100,000 U/kg	IM SC	12
Penicillin V potassium	10–30 mg/kg	PO	6–8
Pentamidine isethionate	15 mg/kg (D)	SC	24 for 2 days
	4 mg/kg (D)	IM, SC	2 wk
Pentazocine	2.2–3.3 mg/kg (C)	IM, IV, SC	Up to every 4
	1.65–3.30 mg/kg (D)	IM, IV, SC	
Pentobarbital	5–15 mg/kg	IV	
	2–4 mg/kg	IV, PO	6
	10–30 mg/kg (D)	IV	2 bolus, remaining to effect
	25 mg/kg (C)	IV	
Pentosan polysulfate	3 mg/kg	IM	7 days
Pentoxifylline			
	10 mg/kg (D)	PO	8
	1.65–3.30 mg/kg (D)	IM, IV, SC	
	400 mg	PO	24–48
Petrolatum, white	1–5 mL/cat	PO	24
Phenamidine isethionate	7.5 mg/kg	IM, SC	24 × 2 days
	15 mg/kg	IM, SC	24 × 1 days
Phenobarbital	2–30 mg/kg (D)	PO, IM, IV	Loading dose (in 3 mg/kg increments)
	6 mg/kg	PO, IM, IV	Every 6
	2–4 mg/kg	IV, PO	12; monitor to adjust dose
	2.2 mg/kg (D)	PO	12
	1–2 mg/kg (D)	PO	8–12
	1 mg/kg (C)	PO	12
	4–8 mg (C)	PO	12 for acute hypertension
Phenoxybenzamine HCl	0.2–1.5 mg/kg (D)	PO	12
	5–15 mg (D)	PO	24 for detrusor areflexia
	10 mg	PO	8–12
	0.5 mg/kg	IV	
	0.25–0.50 mg/kg (D)	PO	6–8 for endotoxemia
	2.5–10.0 mg (C)	PO	24
	0.25 mg/kg (C)	PO	8

Table continued on following page

Table 1. Recommended Dose and Regimen* *Continued*

Drug	Dose†	Route‡	Frequency§
Prednisolone/ prednisone *Continued*	40 mg/m² (D)	PO	24 for 1 wk, then
	20 mg/m² (D)	PO	48 for lymphomas
	0.5 mg/kg (D)	PO	12–24 for hypertrophic osteopathy, panosteitis
	1–4 mg/kg (D)	PO	12 divided for immune-mediated hemolytic anemia or thrombocytopenia
	2 mg/kg (D)	PO, IM	12 for urticaria
	1.1–2.2 mg/kg	PO	12 until remission, then taper for immune-mediated skin diseases
	0.5 mg/kg (D)	PO	12 for 5–10 days, then taper for canine atopy
	4 mg/kg (C)	PO	24 with cyclophosphamide for feline infectious peritonitis
	2.2–6.6 mg/kg (C)	IM, PO, IV, SC	24 initially, then taper to
	2–4 mg/kg (C)		48 for immunosuppression
	15–30 mg/kg (D)	IV	Repeat in 1, 3, 6, or 10, then every other 48 for shock
Prednisolone acetate	0.1–0.2 mg/kg	IM	12
Prednisolone sodium phosphate	11 mg/kg	IV	
Prednisolone sodium succinate	2–4 mg/kg (D)	IV, IM	
	1–3 mg/kg (C)	IV, IM	
	11–30 mg/kg (D)	IV	Repeat in 4–6 for shock
	1–2 mg/kg	IV	
	15–30 mg/kg	IV	Then taper to
	1–2 mg/kg	IV	12
Primaquine PO_4 (Not available in the United States)	0.5 mg/kg (C)	PO, IM	Once
Primidone	55 mg/kg (D)	PO	On first day, then
	10–15 mg/kg (D)	PO	8; monitor for additional dose adjustment
Procainamide	25–50 μg/kg/min (D)	IV infusion	500–1000 mg in 500 mL 5% D/W to effect
	6–8 mg/kg (D)	IV	Over 5 min, then
	6–20 mg/kg (D)	IM	4–6
	8–20 mg/kg (D)	PO	6–8
	6.6–22.0 mg/kg	PO	4 (to 8 if sustained-release preparation)
	62.5 mg/cat	PO	6
	3–8 mg/kg (C)	IM, PO	6–8
Prochlorperazine	1 mg/kg (D)	PO	12
	0.13–0.50 mg/kg (D)	IM	6–8
	0.1 mg/kg	IM	6
	0.13 mg/kg (C)	IM	12
Prochlorperazine/ isopropamide			
Promazine HCl	2.2–6.6 mg/kg (D)	IV	
	2.2–4.4 mg/kg	IM	
	1–2 mg/kg	IM, IV	4–6
	2–4 mg/kg	IM, IV	4–6
Promethazine HCl	0.2–0.4 mg/kg (max. dose: 1 mg/kg)	IV, IM, PO	6–8
Propantheline bromide	0.5–1.0 mg/kg (D)	PO	8
	0.22–0.25 mg/kg	PO	8 up to 3 days
	0.2 mg/kg	PO	6–8
	7.5–30.0 mg (D); size	PO	8
	dependent	PO	24–72; up to every 8
	5.7 mg (C)		
Propiomazine	1.1–4.4 mg/kg	IV, IM	12–24

Table 1. Recommended Dose and Regimen* *Continued*

Drug	Dose†	Route‡	Frequency§
Pyridostigmine bromide	0.2–2.0 mg/kg (D)	PO	8–12; administer anticholinergic first
	7.5–30 mg (D)	PO	12
	<5 kg: 45 mg (D)	PO	6
	5–25 kg: 45–90 mg (D)	PO	6
	>25 kg: 90–135 mg (D)	PO	6
	1–5 mg (C)	IV	
	0.25 mg/kg	PO	24
	0.15–0.30 mg/kg	IM, IV	
Pyrilamine maleate	12.5–25.0 mg	PO	6
Pyrimethamine	1 mg/kg (D)	PO	24
	0.25–1 mg/kg (C)	PO	24
	With sulfonamide at 60 mg/kg (D)	PO	24
	With trimethoprim/sulfonamide at 15 mg/kg (D and C)	PO	12
	0.5–2.0 mg/kg	PO	12 for 14–28 days
	1 mg/kg (D)	PO	24 for 14–28 days
			5 days only for *Neosporum canium*
	2 mg/kg (C)	PO	24 for 14–28 days
Quinacrine	6.6 mg/kg (D)	PO	12 for 5 days
	11 mg/kg (C)	PO	24 for 5 days
Quinidine	4–8 mg/kg (C)	IM	8
	10–20 mg/kg (C)	PO	6–8
Quinidine gluconate	6–20 mg/kg	IM, PO, IV slowly	6–12
	6.6–22 mg/kg	IM	2–4; 8–12 (sustained release)
Quinidine polygalacturonate	6–20 mg/kg (D)	PO	6–8
			275 mg quinidine polygalacturonate = 167 mg quinidine base
Quinidine sulfate	6–20 mg/kg (D)	PO	6; 8 (extended caps)
	6.6–22 mg/kg	PO	Every 2 hr until arrhythmia controlled, then 6–8 300 mg quinidine sulfate = 250 mg quinidine base
Racemethionine	See DL-methionine		
Ranitidine HCl	1–2 mg/kg (D)	PO	12
	2–4 mg/kg (D)	PO	8–12
	0.5 mg/kg	IV, PO, SC	12
	3.5 mg/kg (C)	PO	12
	2.5 mg/kg (C)	IV	12
Retinol (vitamin A)	625–800 IU/kg	PO	24
Ribavirin	11 mg/kg	PO, IM, IV	24 × 7 days
Riboflavin	10–20 mg/day (D)	PO	
	5–10 mg/day (C)	PO	
	5–10 mg/kg (C)	PO	24 × 14 days
Rifampin	10–20 mg/kg	PO	8–12 (D), 24 (C)
Ringer's solution	40–50 mL/kg/day	IV, SC, IP	For maintenance
Roxithromycin	15 mg/kg	PO	24
Rutin	50 mg/kg	PO	8
Scopolamine hydrobromide	0.03 mg/kg (D)	SC, IM	6
Selegiline	0.5 mg/kg	PO	24
	1–2 mg/kg	PO	24
Selamectin	6 mg/kg	Topical	30 days
			1–2 × 30 days apart
			Once
Selenium	0.1 mg/kg	IV infusion	
Selenious acid, sodium selenite	0.3 mg/kg	PO	
Senna	5 mL/cat (syrup)		24
	1/2 tsp/cat with food (granules)		24
Silver nitrate solution 0.5%	Saturate wet dressings		12–24
Silver sulfadiazine	Apply light coating		12 for several days, then 24
	Dilute 1:1 with water	Pack cleaned ears	12
Skin So Soft by Avon	1.5 oz/gal water (D)		Use as a dip once weekly

Table 1. Recommended Dose and Regimen* *Continued*

Drug	Dose†	Route‡	Frequency§
Sodium aurothiomalate	0.5 mg/kg (D)	IM	Once a wk for 6 wk
Sodium bicarbonate	10–15 mg/kg	PO	8
	50 mg/kg (1 tsp is approx 2 g)	PO	8–12
	0.3 × wt (kg) × (target bicarb-part bicarb)		Dose for acidosis
	0.5–1.0 mEq/kg (8.5% solution = 1 mEq/ml of $NaHCO_3$)	IV	Dose for acidosis
	2–3 mEq	IV	Over 30 min
	0.65–5.85 g	PO	Maintain pH 7.0 up to 7.5
Sodium chloride	1–5 g/day	PO	
	1–4 g/day	PO	8 divided daily
	0.5–1.0 g/day (D)	PO	
	40–50 mL/kg/day	IV, SC, IP	
Sodium chloride 5% 0.0 (Muro 128)	Apply 1/8 inch	Topically	2–6 times daily
Sodium chloride 7.5%	2–8 mL/kg	IV	To be followed with balanced crystalloids
Sodium iodide, 20% solution	0.5 mL/5 kg/day (C)	PO	
	20–40 mg/kg (D)	PO	8–12 for 4–6 wk
	20 mg/kg/day (C)	PO	For 4–6 wk
Sodium phosphate	Dilute 1–3 g with water (1:1); give 10–20 mL	PO	8–24 until stools are soft
Sodium polystyrene sulfonate	8–15 g	PO	8
	2 g/kg in 3–4 mL H_2O	PO	Divided every 8 hr
	15 g in 100 mL of 1% methylcellulose or glucose		Rectal
Sodium stibogluconate; antimony	30–50 mg/kg (D)	IV, SC	24 for 3–4 wk
Sodium sulfate	1 g/kg (D)	PO	
	50 mg/kg in 1.5% solution in water (C)	IV	4 for 6 treatments
	5–20 g (D)	PO	
	2–5 g (C)	PO	
Sodium, thiopental	3–15 mg/kg	IV	To effect
Sodium thiosulfate 20%	40–50 mg/kg (D)	IV	8
Sorbitol	3 mL/kg	PO	
Sotalol	1–2 mg/kg	PO	12
Spectinomycin	5–12 mg/kg	IM	12
	20 mg/kg (D)	PO	12
Spiramycin	Susceptible infections		
	12.5–23 mg per dog or cat	PO	24
Spironolactone	1–2 mg/kg (D)	PO	12
	2–4 mg/kg/day	PO	
	1 mg/kg (C)	PO	12
	12.5 mg (C)	PO	24
Spironolactone/ hydrochlorothiazide	2 mg/kg	PO	12–24
Stanozol	2–10 mg (D)	PO	12 as anabolic agent
	1–2 mg (C)	PO	12
	0.5–2.0 mg (C)	PO	24 for anemia
	10–25 mg/kg (C)	PO	7 days
	1–4 mg (D)	PO	24
	25–50 mg/dog/wk	IM	7 days
	1 mg/cat	PO	12
	25 mg (C)	IM	7 days
	1–4 mg (C)	PO	12
Staphage lysate	0.1–0.2 mL	SC	Then
	Incremental doses to 1.0 mL (up to 1.5 mL in large dogs if necessary)		1–2 for 1 wk
	0.5 mL	SC	Weekly for 10–12 wk, then every 1–2 wk increasing the dosing
	0.5–1.0 mL		
	Interval to the longest that maintains clinical control		

Table continued on following page

Table 1. Recommended Dose and Regimen* *Continued*

Drug	Dose†	Route‡	Frequency§
Staphylococcus A	20 μg/2.75 kg	IP	3.5 days or twice weekly
Streptomycin (dihydrostreptomycin)	10 mg/kg (D)	IM	6–12
	3–5 mg/kg with minocycline (D)	IM	12
	10–20 mg/kg (C)	IM	12
Styrid caricide (styrylpyridinium chloride plus diethylcarbamazine)	6.7 mg/kg	PO	24
	diethylcarbamazine and 5.5 mg/kg styrylpyridinium	PO	24
	chloride	PO	24
	No. 20: 1 tab/10 kg (D)	PO	24
	No. 50: 1 tab/25 kg (D)		
Succinylcholine	0.07 mg/kg (D)	IV	
	0.06 mg/kg (C)	IV	
Sucralfate	1 g/25 kg (D)	PO	6–8
	250–500 mg (C)	PO	8–12
	40 mg/kg (C)	PO	8
	0.5–1.0 g (D)	PO	8, 30–60 min after cimetidine
Sufentanil	2 μg/kg (max. dose 5 μg/kg)	IV	
Sulfadiazine	220 mg/kg	PO	For 1 treatment, then
	50–110 mg/kg	PO	12
	15–50 mg/[1, 2] kg/day, with pyrimethamine	PO	Divided 12 for 14 days
	50 mg/kg (loading)		
	25 mg/kg (C)	PO	12
	100 mg/kg (loading)		
	50 mg/kg	IV, PO	12
Sulfadiazine/ trimethoprim[1]	30 mg/kg (C)	PO	24
	15 mg/kg	PO, IV	8–12
	15 mg/kg (D)	PO	8–12 for 14 days
	30–60 mg/kg	PO, SC	12
Sulfadimethoxine	25–50 mg/kg	PO, IM, IV	12–24
	100 mg/kg	PO, IM, IV	
	55 mg/kg (loading)		Followed by
	27.5 mg/kg	PO	24
Sulfadimethoxine/ ormetoprim	27 mg/kg (D)	PO	24 for 14 days
	Day 1: 55 mg/kg, then 27.5 mg/kg (D)	PO	Once daily for a max. of 21 days
Sulfaguanidine	100–200 mg/kg	PO	8 for 5 days
Sulfamerazine	50 mg/kg	PO	12
Sulfamethazine	100 mg/kg (loading)	PO	
Sulfamethoxazole	100 mg/kg (loading)	PO	
	50 mg/kg	PO	12
Sulfamethoxazole/ trimethoprim	15 mg/kg	PO	12
Sulfasalazine	10–30 mg/kg (D) (max. 3 g)	PO	8–12
	10 mg/kg (D)	PO	8 until remission, then taper
	250 mg (C)	PO	8 for 3, then 24 hr
	20–25 mg/kg (C)	PO	12–24
	15 mg/kg	PO	12
Sulfisoxazole[1, 2]	50 mg/kg	PO	8
Sulfobromophthalein sodium	5 mg/kg	IV	Collect serum 30 min after BSP injection
Suprofen 1% ophthalmic solution		Apply topically	8–12
Tamoxifen	i–2 mg/kg (D)	PO	12
Taurine	500 mg (D)	PO	12
	250–500 mg (C)	PO	12
	250 mg (C)	PO	12–24
Teicoplanin	3–12 mg/kg (D)	IV, IM	24
Telazol	6.6 mg/kg (C)	IM	
	11–15 mg/kg (C)	IM	
Temaril-P (trimeprazine plus prednisolone)	0.7–1.1 mg/kg (of trimeprazine)	PO	12–24
Terbinafine	3–10 mg/kg	PO	24
Terbutaline	0.01 mg/kg	SC, IM	4
	2.5–5.0 mg (D)	PO, SC	8
	1.25–2.50 mg (C)	PO	8
Terfenadine	2.5–5.0 mg/kg (D)	PO	12

Table 1. Recommended Dose and Regimen* *Continued*

Drug	Dose†	Route‡	Frequency§
Testosterone cypionate	200 mg (D)	IM	Monthly
	2.2 mg/kg	IM	2–3 days
Testosterone enanthate	1–2 mg/kg; max. 30 mg (D)	IM	Every 2–4 wk
Testosterone (methyltestosterone)	1–2 mg/kg; max. 30 mg/day	PO	Once daily
Testosterone propionate	1–2 mg/kg (D)	SC, IM	2–3 for 1 wk
	12.5 mg with estrogen (C)	IM	
	5–10 mg (C)	IM	
Tetanus toxoid	0.2 mL (test dose)	SC	Watch for anaphylaxis for 30 min
	Then give 30,000–100,000 U (D)	IM, IV	
	100–500 U/kg (max. 20,000 U) (D)		
Tetracycline HCl	10–25 mg/kg (C)	PO	8–12
	Mix 20 mg/kg in 4 mL/kg saline (D)	Infuse into pleural space	
	22 mg/kg (D)	PO	8–12
	10–20 mg/kg (D)	PO	8 for 28 days
	5–10 mg/kg or 50 mg (D)	PO	24
	10 mg/kg (D)	PO	8 for 21 days
	20–22 mg/kg (D)	PO	8 for 14–21 days
	15 mg/kg (C)	PO	8 for 21 days
	22 mg/kg	PO	8
	15 mg/kg (D)	PO	8
	10–25 mg/kg	IV, IM	8–12
	May use capsules or aqueous solution		
Tetramine	10–15 mg/kg (D)	PO	12
Tetramisole	2 mg/kg (D)	SC	For 2–4 treatments
Thenium closylate	2.3–4.5 kg: 250 mg (D)	PO	Every 12 for 1 day, repeat in 2–3 wk
	>4.5 kg: 500 mg (D) (max. 110 mg/kg)	PO	Repeat in 2–3 wk
Theophylline	5–11 mg/kg (D)	PO, IM, IV	6–8
	4 mg/kg (C)	PO, IM	8–12
Theophylline, sustained release	Theo-Dur: 20 mg/kg (D)	PO	12
	20 mg/kg (C)	PO	24, at night
	Gyrocap: 30 mg/kg (D)	PO	2
	Tablets and Gyrocap: 25 mg/kg (C)	PO	24, at night
	Choledyl SA: 47 mg/kg (D)	PO	12
Thiabendazole	10–20 mg/kg (D)	PO	12 for 6 wk
	70 mg/kg (D)	PO	12 for 2 days, then
	35 mg/kg	PO	12 for 20 days
	50 mg/kg (D)	PO	Once daily for 3 days, repeat in 1 month
	125 mg/kg (C)		Every 24 for 3 days
Thiacetarsamide	2.2 mg/kg	IV	12 for 2 days; entire dose should be given in 36 hr
Thiamine	1–2 mg	IM	
	100–250 mg	SC	12 until regression of symptoms
	5–50 mg (D)	IM, SC, IV	
	100–250 mg/kg (C)	SC	12 until regression of symptoms
	10–20 mg/kg (C)	IM, SC	8–12 until signs abate, then
	10 mg/kg (C)	PO	24 for 21 days
Thiamylal sodium	4% solution: 8–10 mg/kg up to 20 mg/kg (D)	IV	In incremental doses
	2% solution (C): same as dog		
	8.8–13.3 mg/kg		
	4.4–6.6 mg/kg		
Thiethylperazine	0.2–0.4 mg/kg (D)	SC	8–12
Thioguanine	40 mg/m^2 (D)	PO	24 for 4–5, then every 3 days
	25 mg/m^2 (C)	PO	24 for 1–5, then every 30 days
Thiopental sodium	10–25 mg/kg (D)	IV	To effect, depending on duration of anesthesia
	15.4 mg/kg	IV	After tranquilization
	11 mg/kg	IV	After narcotic premedication

Table continued on following page

Table 1. Recommended Dose and Regimen* *Continued*

Drug	Dose†	Route‡	Frequency§
Thiotepa	0.2–0.5 mg/m^2 (D)	Intracavitary, IV	
Thioridazine	1.1 mg/kg (D)	PO	
Thyroid	15–20 mg/kg/day	PO	
Thyrotropin (TSH)	5 IU/kg (D)	IV	Collect baseline sample and post-TSH sample at 6 hr
	1 IU/kg (C)	IM	Collect baseline sample and post-TSH sample at 8–12 hr
	1–2 IU	SC	24 for 5 days
L-Thyroxine (T_4, levothyroxine)	22 μg/kg (D) or 0.5 mg/m^2	PO	12
	20–30 μg/kg/day	PO	24 or 12 divided daily
	22 μg/kg (D)	PO	12–24
Ticarcillin	15–25 mg/kg	IM, IV	6–8
	55–110 mg/kg	IM, IV	4–8
Ticarcillin/clavulanate	As above		
Tiletamine/zolazepam	9.9–13.2 mg/kg (D)	IM	Do not exceed 26.4 mg/kg with repeat doses
	9.7–11.9 mg/kg (C)	IM	
	6.6–9.9 mg/kg (D)	IM	
	10.6–12.5 mg/kg (C)	IM	Do not exceed 72 mg/kg with repeat doses
	6–13 mg/kg (D)	IM	For surgeries longer than 30–60 min
	14.3–15.8 mg/kg (C)	IM	
Tinidazole	44 mg/kg (D)	PO	24 for 3 days
	15 mg/kg (C)	PO	24
	15–25 mg/kg (D)	PO	12
Tiopronin	15–20 mg/kg	PO	12
Tobramycin	4–6 mg/kg (D)	SC, IM, IV	12–24
Tocainide	17–20 mg/kg (large D)	PO	8
	30 mg/kg (small D)	PO	8
Tolazoline	15–110 mg/kg (D)	PO	12–24
	2 mg/kg (C)	IV	
Toltrazuril	5–10 mg/kg (D)	SC, PO	24 for 3–5 days
	5–20 mg/kg (D)	PO	24
Toluene	267 mg/kg	PO	Repeat in 2–4 wk
Tretinoin		Topically	24
Triamcinolone	0.25–2.0 mg (D)	PO	24
	0.25–0.50 mg (C)	PO	24 for 7 days
	0.11–0.22 mg/kg	PO, IM, SC	24–48
	2–4 mg (C)	PO	24–48
	0.5–1.0 mg/kg (C)	PO	24
Triamcinolone acetonide	0.1–0.2 mg/kg	IM, SC	24
	Intralesional: 1.2–1.8 mg or 1 mg for every diameter of tumor		Every 2 wk
Triamcinolone ophthalmic solution	4–8 mg (D)	Subconjunctivally	
	4 mg (C)	Subconjunctivally	
Triamterene	1–2 mg/kg (D)	PO	12
Trientine hydrochloride	10–15 mg/kg	PO	12
Triethylenethiophosphoramide	30 mg/m^2	Intravesicularly	Every 3–4 wk
Triethylperazine	0.13–0.2 mg/kg	IM	8–12
Trifluoperazine	0.03 mg/kg	IM	12
Triflupromazine	0.1–0.3 mg/kg	IM, PO	8–12
Trifluridine ophthalmic solution	0.1% solution: 1–2 drops	Apply topically	3–8 times daily
		Apply topically	3–4
Triiodothyronine (T_3)	4–6 μg/kg (D)	PO	8
	4.4 μg/kg (C)	PO	8–12
	<20 kg 2.5 mg (D)	PO	12 for 4 days, then reduce dose by 50%
	>20 kg 15 mg (D)	PO	12 for 4 days, then reduce dose by 50%
Trimeprazine	1.0–2.0 mg/kg (D)	PO	12
	1.1–4.4 mg/kg (D)	PO	8
Trimethobenzamide	3 mg/kg (D)	IM	8–12
Trimethoprim/sulfadiazine	15 mg/kg	PO, SC	12
	15 mg/kg	PO, IV	8–12
	15 mg/kg (D)	PO	8–12 for 14 days
Trimetraxate glucuronate	10 mg/kg (D)	IV	24 for 21 days

Table 1. Recommended Dose and Regimen* *Continued*

Drug	Dose†	Route‡	Frequency§
Vitamin D_3 (calcitriol, 1-25-dihydroxy-vitamin D_3)	0.03–0.06 μg/kg/day	PO	
	0.025 μg/kg/day	PO	
Vitamin E	70 IU/kg (D)	IM	Intermittently
	100–500 IU (D)	PO	24 for 4 wk for malabsorption
	200-800 IU (D)	PO, topically	12
	10–20 IU/kg (C)	PO	12
	400–600 IU	PO	12–24
	500 mg/day (D)	PO	
	100 mg/day (C)	PO	
Vitamin K_1 (phytonadione)	1–3 mg/kg	SC, PO	12, recheck coagulation at 2 days and 3 wk for cirrhosis
	5 mg/kg (C)	IM	12–24
	2.5 mg/kg (small D)	SC (several sites)	Load, then
	0.25–2.5 mg/kg	PO	Divided 8–12
	5 mg/kg (large D)	SC (several sites)	Load, then
	5 mg/kg	PO	Divided 8–12 hr
	2–3 mg/kg (small D)	SC	12, until coagulation normal for acute hepatopathy
	5 mg/kg (large D)	SC	12, until coagulation normal
	15–25 mg (small C)	IV	24 for 7 days
	15–25 mg (large C)	IV	24 for 3–4 wk until coagulation normal, check 1–2 days after therapy discontinued
Warfarin	1 mg/kg/day	SC, PO	5–7 days for short-acting rodenticides
	3–5 mg/kg/day	SC, PO	4–6 wk for long-acting rodenticides
	0.1–0.2 mg/kg (D)	PO	24
	0.06–0.20 mg/kg (C)	PO	24, maintain prothrombin time 2.0–2.5 times normal
Xylazine	1.1 mg/kg (D)	IV	
	1.1–2.2 mg/kg	IM, SC	
	1.1 mg/kg (D)	IM	
	0.44 mg/kg (C)	IM	
Yohimbine HCl	50–100 μg/kg (D)	SC	8–12
	0.11 mg/kg (D)	IV	
	0.25–0.5 mg/kg	SC, IM	12
	0.5 mg/kg (C)	IV	
Zafirlukast	0.15–0.2 mg/kg	PO	24
Zidovudine	5–20 mg/kg (C)	SC, PO	8–12
Zinc acetate	5–10 mg/kg (D)	PO	12
	100 mg (D)	PO	12 for 3 months, then
	50 mg (D)	PO	12
Zinc methionine	1.7 mg/kg (D)	PO	24
Zinc sulfate	10 mg/kg (D)	PO	24
	5–10 mg/kg (D)	PO	12

*Modified from Boothe D: Small Animal Formulary, 5th ed, American Animal Hospital Press, Lakewood, CO, 2000; Plumb DC: Plumb's Veterinary Drug Handbook, 2/E, Iowa State University Press, 1994; Bonagura JD (ed): Kirk's Current Therapy XIII, Philadelphia, WB Saunders, 2000; and Ettinger S, Feldman E (eds): Textbook of Veterinary Internal Medicine, 4/E, Philadelphia, WB Saunders, 1995.

†D = dog; C = cat. Absence of a letter indicates that the dosage is recommended for both the dog and the cat.

‡PO = oral; IM = intramuscular; IP = intraperitoneal; SC = subcutaneous; IT = intratracheal; IV = intravenous; SC = subcutaneous; IO = intraosseous.

§Numbers refer to hours unless otherwise indicated.

¶GSD = German shepherd dog; GSDx = German shepherd dog cross.

Variable dogs reflect different routes and indications.

Table 2. Constant Intravenous Infusion Rates[1] *Continued*

Drug	Loading Dose	Maintenance Dose	Diluent
Norepinephrine bitartrate		0.05–0.2 µg/kg/min	5% Dextrose[2]
Oxytocin		5–10 U over 30 min (dog) 2–5 U over 30 min (cat)	5% Dextrose or 0.9% NaCl
Pancuronium bromide	0.04–0.1 mg/kg	0.06–0.1 mg/kg/hr	5% Dextrose or 0.9% NaCl
Pentobarbital sodium	3–15 mg/kg (to effect)	0.2–1 mg/kg/hr	5% Dextrose of 0.9% NaCl[2]
Phentolamine			
Phenylephrine		1–3 µg/kg/min	5% Dextrose of 0.9% NaCl
Potassium chloride		In IV fluids: 28–80 mEq/L, not to exceed 0.5 mEq/kg/hr	Any IV fluid
Potassium phosphate		0.01–0.03 mM/kg/hr for 6 hr	0.9% NaCl
Procainamide	6–8 mg/kg over 5 min	25–50 µg/kg/min	0.9% NaCl
Sodium bicarbonate		50% of calculated dose (based on deficit) IV over 4–6 hr	5% Dextrose or 0.9% NaCl[2]
Vitamin B complex		2–4 mL/L at maintenance fluid rate	

Sources for Tables 1 and 2 are the same.

IV = intravenous.

1. Administration of an IV drug is inherently associated with greater risk of adverse events. Become familiar with the contraindications and risks of drug administration. In general, diluted solutions should be used within 24 hours. To calculate the rate of fluid administration to a patient:
   a. Dose infused (mg/kg/hr): Drug dose = (mg/kg) × (hrs) × body weight (kg) × time of infusion.
   b. Calculate total amount of fluids to be administered during the time of infusion: Fluid dose fluids (mL/kg/hr) = dose (mL/kg) × body weight × time of infusion.
   c. Add the calculated amount of drug to the calculated amount of fluid. To adjust to a convenient volume (e.g., 500 mL/fluid), multiply the calculated dose proportionately: Drug dose (mg)/fluid dose (mL) = A/500 mL + B, where A is the mg to be calculated and B is the volume to be added to 500 mL of fluid.
   d. The prepared solution should be administered at the rate decided in B.
2. Potential drug incompatibilities should preclude mixing this drug with other drugs.
3. Due to drug incompatibilities, do not combine with sodium bicarbonate.
4. Do not use if solution becomes cloudy.
5. Drug will bind to polyvinyl plastic of IV lines; flush fluid lines with approximately 50 mL of prepared solution and use short infusion lines.
6. Protect solution from light.
7. Slight pink discoloration is expected.
8. Extravasation may cause necrosis and sloughing. Treat extravasated area with 5–10 mg phentolamine prepared in 10–15 mL 0.9% NaCl.
9. Use lower dose in cats. Adjust dose based on activated partial thromboplastin time (1.5-fold to 2.5-fold increase). Loading dose can be administered IV or, for disseminated intravascular coagulopathy, in appropriate blood replacement product after a 30-minute incubation.
10. Use drug with extreme caution. Use with infusion pump only; death due to cyanide toxicity may occur.

Index

Page numbers in *italics* refer to illustrations; page numbers followed by t indicate tables.

A

Abbreviations, for prescriptions, 709t
Abdominal infection, 203–205
ABPP (bropirimine), 364
Abscesses, organisms causing, 128t
Absorption, drug, 6–7, *6, 7*
  antimicrobial efficacy and, 142
  changes in, in cardiac disease, 28
  drug interactions involving, 22, 22t
  food's effects on, 19, 22t
  in pediatric animal, 30–32, 31t
  in plasma concentration vs. time curve, 4, *5*
  percutaneous, 655–656
  species and breed differences in, 35
  in small intestine, 496
Absorption half-life, 7
Absorption rate constant, *5*, 7
Acarbose, 644, 733t
Accumulation, drug, *14*, 15–16, 15t, 435
  dosing regimen extrapolation and, 37–38
Accumulation ratio, 63, *68*
Acemannan, 354t, 363, 733t
Acepromazine, adverse effects of, 461
  as preanesthetic medication, 425–426
  dosage for, 413t, 459t, 733t
  for feline urologic syndrome, 549
Acetaminophen, 295–296
  codeine with, dosage for, 413t, 733t
  dosage for, 284t, 733t
  hematologic disorders due to, 56, *56*, 56t
  hepatotoxicity of, 36, *46*, 47, 295
    ascorbic acid for, 295, 484t
  intoxication with, 719t
Acetazolamide, 519t, 522
  dosage for, 521t, 733t
  site of action of, *516*
  structure of, *518*
Acetic acid, for *Malassezia* infection, 233
  for otitis externa, 197
  for otitis media, 178
Acetohydroxamic acid, 733t
Acetylation, in drug metabolism, 10
  species differences in, 36
Acetylcholine, 458, 473
  in control of airway caliber, 602, *603*
  in gastric acid secretion, 489, *489*
  in heart rate regulation, 567
  in vomiting reflex, 483, *486*
Acetylcysteine, 733t
  as mucolytic agent, 613
    with antimicrobial therapy, 182–183, 184
  for acetaminophen toxicity, *46*, 47, 295
  for acute liver failure, 509
Acetylsalicylic acid. See *Aspirin (acetylsalicylic acid).*
Achlorhydria, due to gastric antisecretory drugs, 489–490
Acid citrate dextrose, for stored blood preservation, 100
Acid ingestion, 719t
Acid-base status, 75–94. See also *Metabolic acidosis; Metabolic alkalosis.*
  disease-induced changes in, 81–82, 81t
    treatment of, 87–88
  evaluation of, 82
  maintenance of, 77–78
Acidification of urine, adverse effects of, 548
  ammonium chloride for, 521t, 526
  drugs for, 526
  for feline urologic syndrome, 548
Acidosis, metabolic. See *Metabolic acidosis.*
  respiratory, 81t, 82
    pathophysiology of, 78
    treatment of, 88
Acral lick dermatitis, 469, 673
Acromegaly, 650
Acrylic beads, antibiotic-impregnated, for osteomyelitis, 180
ACTH. See *Corticotropin (ACTH).*
Actinomycin D (dactinomycin), 341, 733t, 740t
Actinomycosis, 209–210, 621
Action potential of cardiac muscle, 555–556, *556*
Activated charcoal, 499
  dosage for, 484t, 733t, 738t
  preparations of, 718t
Active transport, drug movement by, 6
  in biliary excretion, 11
  in renal tubules, 10, *11*
Acyclovir, *239*, 241, 733t
  for ocular herpetic infection, 247
ADCC (antibody-dependent cell-mediated cytotoxicity), 351
S-Adenosylmethionine (SAMe), for liver disease, 502
  for osteoarthritis, 301
Adenylate cyclase, in myocardial contractility regulation, *554*, 555
Adequan (polysulfated glycosaminoglycans), dosage for, 284t
  for osteoarthritis, 297–299
  for septic arthritis, 181
  for urinary tract infection, 189
Adhesins, bacterial, in gastrointestinal disease, 202
    in urinary tract infection, 185
Administration, route of. See *Route of administration;* specific routes.
Adrenal disorders, 644–649. See also *Hyperadrenocorticism; Hypoadrenocorticism.*
α-Adrenergic agonists. See also specific drugs.
  as decongestants, 614
  for hypotonic urethra, 545
  for hypovolemic shock, problems with, 89
  α_2-selective, as preanesthetic medications, 426–427
    for diarrhea, 498
    for pain, 418–419
β-Adrenergic agonists. See also specific drugs.
β-Adrenergic agonists *(Continued)*
  as bronchodilators, *603, 604*, 606–607, 608t
  as inotropes, 578–579
  digoxin interaction with, 575
  for dilated cardiomyopathy, 583
α-Adrenergic blockers. See also specific drugs.
  for hypertonic urethra, 546
β-Adrenergic blockers. See also specific drugs.
  as antiarrhythmics, 571–572
  for atrial fibrillation, 587
  for behavioral modification, 468
  for dilated cardiomyopathy, 583
  ototoxicity of, 52
Adrenergic receptors, in cardiovascular system, *554*, 555
  in gastric motility, 494
Adrenocorticotrophic hormone. See *Corticotropin (ACTH).*
Adsorbents, as vehicles for topical drugs, 657
  gastrointestinal, 499. See also specific drugs.
Adverse drug reactions, 41–58
  cytotoxic, 41, *42*
  defined, 41
  reducing incidence of, 57
  reporting of, 57–58, 699–701, *700–701*
  type A, 3, 41, *42*
    organs most susceptible to, 42
  type B, 3, 41, 43–44. See also *Hypersensitivity.*
    organs most susceptible to, 42
Aelurostrongylus infection, 619
Aerosol sprays. See *Sprays.*
Aerosolization, drug administration by, 613, 614–615, 615t
Agar plate method, for culture and susceptibility testing, 130, *130*
Age. See also *Geriatric animals; Neonates; Pediatric animals.*
  drug disposition differences due to, 29–34
  response to pain and, 407
Aggression, anticonvulsants for, 467, 469
  benzodiazepines for, problems with, 467, 469
  dominance-related, 469
  in cats, 471–472
  phenothiazines for, problems with, 461
  toward new dog, 469
Agranulocytosis, due to methimazole, 630
Agriculture Department (U.S.), reporting adverse biologic product reactions to, 699
Airway smooth muscle, control of tone of, 602–603, *603*
  heparin's effects on proliferation of, 119
Akathisia, due to phenothiazines, 460
Akinesia, defined, 407
Albendazole, 270–271, 733t
  for giardiasis, 264–265, 507
  for parasitic lung disease, 619
  for protozoal infections, 258t
Albumin. See also *Hypoalbuminemia.*
  calculating deficit of, for plasma infusion, 104

Albumin *(Continued)*
  hormonal drug effects involving, 55
  in water distribution, 76
  serum, in geriatric animal, 30
    in pediatric animal, 32
  with diuretic therapy, in nephrotic syndrome, 525
Albuterol, 607, 608t, 733t
Alcohols. See also specific agents.
  as germicides, 251, *251*
    for surgical antisepsis, 256
Aldactazide, 733t
Aldehyde compounds, as germicides, *251*, 252
Aldosterone, heparin's effects on, 120
  in regulation of renal electrolyte transport, 76, 77, 516, *517*
  mechanism of action of, 315
  structure of, *320*
Aldosterone antagonists, *517*, 519t, 523–524
Aldosterone-induced proteins, 523
Alfaxalone (Althesin), 453
Alginic acid, for gastroesophageal reflux, 504
Alkali ingestion, 719t
Alkalinization of urine, acetazolamide for, 522
  sodium bicarbonate for, 521t, 526
Alkalinization therapy, for chronic renal failure, 534t, 536
Alkaloid intoxication, 719t
Alkalosis, metabolic, 81t, 82
    due to furosemide, 524
    pathophysiology of, 78
    treatment of, 88
  respiratory, 81t, 82
    pathophysiology of, 78
    treatment of, 88
Alkylating agents, 336–338. See also *Anticancer drugs; Chemotherapy;* specific drugs.
Allergy. See *Hypersensitivity.*
Allopurinol, dosage for, 521t, 733t
  for shock, 590t
  for urate urolithiasis, 521t, 526–527
Allylamine antifungals, 231. See also *Terbinafine.*
Aloe vera cream, 733t
Alopecia, drug-induced, 53
  due to anticancer drugs, 336
  psychogenic, in cats, 472, 672
Alpha agonists. See α-Adrenergic agonists.
Alpha blockers. See also specific drugs.
  for hypertonic urethra, 547
Alpha Keri, 733t
Alpha-glucosidase inhibitors, for diabetes mellitus, 644
Alprazolam, 459t, 467, 734t
  for noise phobias, 470
Alternaria alternata, drug susceptibilities of, 223t
Alternative health agents, adverse reactions to, 42
Aluminum carbonate, 534t, 536, 733t
Aluminum hydroxide, as antacid, 492
  as phosphorus binder, 536
  dosage for, 484t, 534t, 733t
Aluminum magnesium hydroxide, 733t
Amantadine, 243
Amebiasis, 508
Amikacin, 159, 160
  aerosol therapy with, 615t
  bronchial penetration by, 182t
  dosage for, 154t, 177t, 734t
  for actinomycosis and nocardiosis, 209
  for pyothorax, 184
  for surgical prophylaxis, 219
  for urinary tract infections, 187t
  in pediatric animal, 33
Amikacin *(Continued)*
  minimum inhibitory concentrations for selected organisms for, 132t
  relative efficacy of, *133*
  structure of, *159*
  susceptibility test interpretation for, 134t
  therapeutic monitoring data for, 63t
Amiloride, 519t, 523
  dosage for, 521t
Amino acids, essential and nonessential, 713t
  parenteral solutions of, interactions with, 20t
γ-Aminobutyric acid (GABA), 457–458
Aminocaproic acid, 118, 734t
Aminoglycosides, 151t, 158–162. See also specific drugs.
  adverse effects of, *42*, 160–162, *161*
    plasma drug concentrations and, 144
  bronchial penetration by, 182
  central nervous system toxicity of, 51, 51t
  drug interactions with, neuromuscular blockers, 476t
    penicillins, 19, 146
  efficacy of, host factors affecting, 140
    in anaerobic environment, 215
  for peritonitis, 204
  for pyoderma, 194, 195
  for urinary tract infections, 187t, 188
  in pediatric animal, 33
  intensive fluid therapy with, case study of, 70
  mechanism of action of, 158, *159*
  nephrotoxicity of, *42*, 48, 160-162, *161*
    furosemide and, 524, 529
  ototoxicity of, 51–52, 162
  parenteral solutions of, interactions with, 20t
  passive diffusion of, 5–6
  pharmacokinetics of, 160
  postantibiotic effect of, 66, 137, *138*
  resistance to, 160
  safety of, for developing fetus, 190
  spectrum of activity of, 152t, 158–160
  structure of, 158, *159*
  therapeutic monitoring of, artifacts in, 72t
Aminopentamide, *487*, 734t
Aminophylline, 607
  adverse reactions to, 609
  dosage for, 608t, 734t
  for bronchial disease, 617
  parenteral solutions of, interactions with, 20t
  to facilitate aerosol drug delivery, 615
Aminopromazine, 549, 734t
Aminosalicylic acid, 290, 734t
  thyroid effects of, 54t
21-Aminosteroids, 306–307, *307*, 322
Amiodarone, 562t, 572, 734t
Amitraz, 663, 734t
  central nervous system toxicity of, 50, 51t
  for demodicosis, 674
  tricyclic antidepressant interaction with, 464
Amitriptyline, 462, 464
  dosage for, 413t, 459t, 665t, 734t
  for feline urologic syndrome, 549
  for inappropriate elimination in cats, 471
  for pain, 419
  for skin diseases, 665t, 668
Amlodipine, 561, 564–565
  dosage for, 562t, 734t
  for hypertension, 586
Ammonium chloride, dosage for, 521t, 734t
  for urine acidification, 526
    in feline urologic syndrome, 547
Amoxicillin, 158. See also *Amoxicillin–clavulanic acid.*
  bronchial penetration by, 182, 182t
  dosage for, 154t, 734t
  for anaerobic infections, 215
Amoxicillin *(Continued)*
  for *Helicobacter* infection, 505
  for kennel cough, 617
  for pyothorax, 184
  for surgical prophylaxis, 219
  for urinary tract infections, 187t
  minimum inhibitory concentrations for selected organisms for, 132t
  pharmacokinetics of, 157
  relative efficacy of, *133*
  spectrum of activity of, 152t, 156
  susceptibility test interpretation for, 134t
Amoxicillin–clavulanic acid, 158
  dosage for, 154t, 734t
  for actinomycosis and nocardiosis, 209–210
  for anaerobic infections, 215–216
  for pyoderma, 193, 194, 195
  for pyothorax, 184, 621
  minimum inhibitory concentrations for selected organisms for, 132t
  relative efficacy of, *133*
  spectrum of activity of, 152t, 156
  susceptibility test interpretation for, 134t
Amphetamine, 734t
  intoxication with, 719t
Amphotericin B, 223–227
  adverse effects of, 225–226, *225*
  aerosol therapy with, 615t
  dosage for, 232t, 734t
  drug interactions with, cyclosporine, 356
    digoxin, 575
    thiazide, 523
  for blastomycosis, 233
  for candidiasis, 233
  for coccidioidomycosis, 234
  for cryptococcosis, 234
  for histoplasmosis, 233, 507
  for shock, 591
  mechanism of action of, 224, *225*
  nephrotoxicity of, 49, 225–226, *225*
  parenteral solutions of, interactions with, 20t
  pharmacokinetics of, 225, *225*
  preparations of, 225, 226–227
  resistance to, 224–225
  rifampin with, 171
  spectrum of activity of, 223t, 224
  structure-activity relationship of, 223–224, *224*
  therapeutic use of, 226–227
  topical, 662
Ampicillin, 156, 157
  bronchial penetration by, 182, 182t
  dosage for, 154t, 177t, 734t
  for anaerobic infections, 215
  for hepatic encephalopathy, 509
  for pyothorax, 184
  for urinary tract infections, 187t
  minimum inhibitory concentrations for selected organisms for, 132t
  parenteral solutions of, interactions with, 20t
  skin lesions due to, 53, 53t
  susceptibility test interpretation for, 134t
Ampicillin-sulbactam, 734t
Amprolium, 734t
  for coccidioidomycosis, 507
  for coccidiosis, 261
  spectrum of activity of, 258t
Amrinone, 562t, 577, 734t
  for dilated cardiomyopathy, 583
Amyloidosis, renal, 541
Anabolic steroids. See also specific agents.
  as hematinic drugs, 113–116
    for anemia of chronic renal failure, 115, 540
  structure of, 113, *114*
  thyroid effects of, 54t

- Anaerobic infections, 213–217
  - antimicrobial selection for, 214–216
- Analgesia. See also *Pain;* specific analgesic drugs and classes of drugs.
  - after head trauma, 453
  - defined, 407
  - dosages for, 413t
  - epidural, 413t, 422
  - in pediatric animal, 33–34
  - patient-controlled, 418
- Analgesic nephropathy, 48, 288
- Anaphylactoid reaction, 44, 352
  - to antimicrobials, 144
  - to diethylcarbamazine, 273
  - to thiacetarsamide, in cats, 598
  - treatment of, 364–365
- Anaphylaxis, 43–44, 352, *352*
  - drug-induced, dermatologic manifestations of, 53
  - due to amphotericin B, 226
  - pulmonary manifestations of, in cat, 57
  - treatment of, 364–365
- Androgens. See also specific agents.
  - thyroid effects of, 54t
- Anemia, 107–116
  - aplastic, cyclosporine for, 358
    - due to sulfonamides, 168
  - hemolytic, anabolic steroids for, 115
    - due to hypophosphatemia, 87
    - immune-mediated, 365
      - glucocorticoids for, 326
  - in acute renal failure, 532
  - in chronic renal failure, 534t, 539–540
    - anabolic steroids for, 115, 540
    - erythropoietin for, 111–112
  - pernicious, 108
  - "shotgun" hematinic preparations for, 110
- Anesthesia. See also *Anesthetics;* specific agents.
  - after head trauma, 453
  - defined, 407
  - dissociative, 427–428
  - general, defined, 407
  - in pediatric animal, 33–34
  - premedication for, 425–427
- Anesthetics, 425–430. See also *Anesthesia;* specific agents.
  - inhalant, 428–430
    - hepatotoxicity of, 45
    - in pediatric animal, 31–32, 34
    - neuromuscular blockers' interactions with, 476t
  - injectable, 427–428
    - neuromuscular blockers' interactions with, 476t
  - local, 419
    - in critically ill animals, 420–421
    - intoxication with, 722t, 723t
    - ototoxicity of, 52
  - thiazide interaction with, 522
- Angioedema, drug-induced, 53
- Angiotensin-converting enzyme inhibitors, 565–566. See also specific drugs.
  - adverse effects of, 566
  - for dilated cardiomyopathy, in cats, 584
    - in dogs, 583
  - for hypertension, in chronic renal failure, 539
    - in glomerular disease, 541
  - for renal disease, 565–566
  - renal dysfunction due to, 48–49, 528, 566, *567*
- Anhydrous bases, as vehicles for topical drugs, 656
- Anorexia, due to anticancer drugs, 335, 340
  - in chronic renal failure, 534t, 538
- Antacids, as antiemetics, 488
  - for gastrointestinal ulceration, 492–493
  - iron interaction with, 110
- Antagonism, in antimicrobial therapy, 146–147, *146*
- Antazoline, 734t
- Anthelmintics. See *Heartworm disease; Helminth infections;* specific drugs and classes of drugs.
- Antiarrhythmic drugs, 569–573. See also specific drugs and classes of drugs.
  - class I, 569–571
  - class II, 571–572
  - class III, 572
  - class IV, 572–573
  - classification of, 568
  - for dilated cardiomyopathy, 582–583
  - mechanisms of action of, 567, 568, *568*
  - proarrhythmic effect of, 568
- Antibiotics. See also *Antimicrobial(s);* specific drugs and classes of drugs.
  - defined, 125
- Antibodies, antinuclear, in infective endocarditis, 203
  - immunotherapy using, 362
  - limitation of growth factor therapy by, 377–378, 392, *392*, 393, 540
  - monoclonal, recombinant, 398
  - to insulin, 641–642
- Antibody-dependent cell-mediated cytotoxicity (ADCC), 351
- Anticancer drugs, 336–347. See also *Chemotherapy;* specific drugs and classes of drugs.
  - as immunosuppressants, 359
  - cell kill kinetics for, 331, 331t
  - classification of, 331
  - criteria for response to, 331–332
  - development of, 333
  - dose calculation for, 333–334, 333t
  - dose intensity vs. response for, 334
  - extravasation of, 335–336
  - gastrointestinal disease due to, 50, 335
  - glucocorticoids with, 325–326
  - hematologic disorders due to, 56, 56t, 334–335
    - body surface area and, 333–334
  - hospital personnel and owners' exposure to, 336
  - side effects of, 334–336
  - skin lesions due to, 53, 53t, 336
- Anticholinergic agents. See also specific drugs.
  - adverse effects of, 545
  - as antiemetics, 488
  - as bronchodilators, 608t, 609–610
  - as preanesthetic medications, 425
  - as spasmolytics, 496–497, *497*
  - for acute diarrhea, 506
  - for hypercontractile bladder, 545
  - for irritable bowel syndrome, 507–508
- Anticholinesterases. See also specific drugs.
  - for neuromuscular blockade reversal, 479, 479t
  - intoxication with, 720t
  - neuromuscular blockers' interactions with, 476t
- Anticoagulants, 118–122. See also specific drugs.
  - drug interactions with, furosemide, 524
    - thiazide, 522
  - hematologic disorders due to, 56, 56t
  - in collected blood, 99–100
    - overdose in recipient due to, 104
  - intoxication with, 721t
- Anticonvulsants. See also specific drugs.
  - adrenocortical effects of, 54t
- Anticonvulsants *(Continued)*
  - adverse reaction to, *42*
  - drug interactions with, 434
    - neuromuscular blockers, 476t
  - for acute seizure management, 437–438
  - for aggression, 467, 469
  - for behavioral modification, 467
  - for chronic seizure control, 438–439
  - for pain, 419
  - hepatotoxicity of, 45–47, *46*, 434, 439
  - pharmacokinetics of, 433–436, 435t
  - prophylactic, after head trauma, 453
  - rectal administration of, for acute seizure management, 438
  - structure of, *433*, *434*
  - therapeutic monitoring with, 436–437, *437*, *438*
  - thyroid effects of, 54t, 55
- Antidepressants, 462–466. See also specific drugs and classes of drugs.
  - central nervous system toxicity of, 51, 51t
  - for destructive behavior, 470
  - for skin diseases, 668
  - tricyclic, 462–464
    - antidiuretic hormone secretion and, 526
    - for pain, 419
    - intoxication with, 725t
    - mechanism of action of, *458*, 462
    - monoamine oxidase inhibitor interaction with, 464
    - opioid interactions with, 412
    - ototoxicity of, 52
    - poisoning with, 463–464
    - structure of, *460*, 462
    - withdrawal from, 463, 464
- Antidiabetic agents. See also *Insulin;* specific drugs and classes of drugs.
  - oral, 643–644
- Antidiuretic hormone (vasopressin), 525–526, 650. See also *Desmopressin (DDAVP).*
  - adrenocortical effects of, 54t
  - dosage for, 753t, 773t
  - urinary free water loss and, 76
- Antiemetics, 486–488, *487*. See also specific drugs.
  - for acute diarrhea, 505
  - for acute gastritis, 504
  - for acute pancreatitis, 511
- Antifungal agents, 222–234. See also specific drugs and classes of drugs.
  - factors leading to failure of, 222–223
  - for otitis externa, 198, 198t
  - minimum inhibitory concentrations for, 223, 223t
  - resistance to, 223
  - synergism of, 225, 228
  - therapeutic use of, 231–234, 232t
- Antigen presentation, 350, *351*
- Antigestagens, 680
- Antihistamines. See also specific drugs.
  - central nervous system toxicity of, 51t
  - for allergic rhinitis, 614
  - for behavioral modification, 468
  - for pruritus, 671–672
  - for respiratory disease, 611
  - for skin diseases, 665t, 666
  - H$_2$. See *Histamine*$_2$*-receptor antagonists.*
  - intoxication with, 719t
  - topical, 661
- Antihypertensive drugs. See also specific drugs and classes of drugs.
  - antipsychotic interactions with, 461
- Anti-inflammatory drugs, 281–307. See also specific drugs and classes of drugs.
  - for respiratory disease, 610–611
  - for shock, 304

Anti-inflammatory drugs *(Continued)*
  nonsteroidal. See *Nonsteroidal anti-inflammatory drugs (NSAIDs);* specific drugs.
Antileukemic activity, in blood components, 362
Antimetabolites, 342–344. See also *Anticancer drugs; Chemotherapy;* specific drugs.
Antimicrobial(s), 150–172. See also *Antimicrobial therapy;* specific drugs and classes of drugs.
  acrylic beads impregnated with, for osteomyelitis, 180
  aerosol therapy with, 615t
  antitumor, 339–342. See also *Anticancer drugs; Chemotherapy;* specific drugs.
  bactericidal vs. bacteriostatic, 137–139, 138t, 141
  classification of, 151t, *152*
  criteria for selection of, 125t
  defined, 125
  dose calculation for, *138*, 145–146
    from susceptibility data, 137–138, *138*
  doses of, 154t–155t
  for bacterial enteritis, 506
  for bacterial overgrowth in short bowel syndrome, 507
  for hypovolemic shock, 89
  for parvovirus-associated bacteremia, 506
  for pruritus, 671
  for skin diseases, 664, 665t
  mechanisms of action of, 141, *141, 152*
  minimum inhibitory concentrations of, for selected organisms, 132t
  neuromuscular blockers' interactions with, 476t
  relative efficacy of, *133*, 136–137
  resistance to, 143–144
    pulse dosing and, 195
    topical therapy and, 145, 146
  standards for susceptibility test interpretation for, 134t–135t
  topical, 659t, 661–662
Antimicrobial therapy. See also *Antimicrobial(s);* specific drugs and classes of drugs.
  chemotherapeutic triangle for, 125, *126*
  combination, 146–148, *146, 147,* 147t
  cost and convenience of, 148
  culture and susceptibility testing for, 130–139. See also *Culture and susceptibility testing.*
  decisions to be made during, 125t
  determining need for, 125–126
  diarrhea associated with, 201
  dose calculation for, *138*, 145–146
    from susceptibility data, 137–138, *138*
  dose-dependency vs. time-dependency in, 138, *138*
  drug factors affecting, 141–143
  duration of, 148
  empirical, 126–130, *126*, 127t–128t, *129*
  enhancing efficacy of, 145–148, *146, 147,* 147t
  evaluating response to, 148
  for acute pancreatitis, 511
  for chemotherapy-related infection, 334–335
  for chronic bronchitis, 618
  for chronic liver disease, 510, 511
  for empyema, 621
  for kennel cough, 616–617
  for shock, 591
  host factors affecting, 139–141, 139t, *140*
  in pediatric animal, 33
  microbial factors affecting, 139, *139*
  pharmacokinetic factors in, 142–143, 142t
  postantibiotic effect in, 66, 137, *138*
Antimicrobial therapy *(Continued)*
  principles of, 125–148
  prophylactic, 217–219
    for dental procedures, 200
    for surgery, 218–219
    in granulocytopenia, 218, 334
  relative efficacy of drugs in, *133*, 136–137
  resistance to, 143–144
    pulse dosing and, 195
    topical therapy and, 145, 146
  target organism identification for, 126–139, *126*
  topical, development of resistance and, 145, 146
    toxicity due to absorption in, 145
  toxicity of, 144–145
Antimony, 734t
Antimuscarinic agents. See also specific drugs.
  as antiemetics, 486–487
  as spasmolytics, 497
Antineoplastic drugs. See *Anticancer drugs; Chemotherapy;* specific drugs and classes of drugs.
Antinuclear antibodies, in infective endocarditis, 203
Antioxidants, 305–307. See also specific drugs.
Antiparasitic drugs, 267–277. See also *Heartworm disease; Helminth infections;* specific drugs and classes of drugs.
  for skin diseases, systemic, 665t, 668–669
    topical, 662–663
Antiplatelet agents, 123. See also specific drugs.
Antiprotozoal drugs, 258t. See also specific drugs.
Antipruritics. See also specific drugs.
  topical, 658t, 661, 670–671
Antipsychotic drugs, 458–462. See also specific drugs and classes of drugs.
  adverse effects of, 461
  clinical indications for, 461–462
  disposition of, 461
  drug interactions with, 461
  pharmacologic effects of, 460–461
  structure-activity relationships of, 460
Antiseborrheics, topical, 657–659, 658t
Antisense technology, 399
Antisepsis. See also *Antiseptics;* specific agents.
  factors affecting, 254–255
  procedures for, for surgery, 255–256
    for wounds, 256–257
Antiseptics, 250–257, 251t. See also *Antisepsis;* specific agents.
  characteristics of, by chemical type, 251–254
  defined, 250
  for surgical preparation, 256
  for wounds, 256–257
  targets for, *251*
  urinary, for feline urologic syndrome, 547
    hematologic disorders due to, 56, 56t
Antiserum, for sepsis syndrome, 207
Antispasmodic agents, 479–480, 496–497, *497*. See also specific drugs.
  for feline urologic syndrome, 547–548
Antithrombin III, heparin binding to, 118–119, *119*
Antithrombotics, 123. See also specific drugs.
Antitoxin, for botulism, 217
  for tetanus, 217
Antitumor antibiotics, 339–342. See also *Anticancer drugs; Chemotherapy;* specific drugs.
Antitussives, 608t, 611–612. See also specific drugs.
Antitussives *(Continued)*
  intoxication with, 719t
Anti-ulcer drugs, 488–493. See also specific drugs.
Antivenins, 724t, 734t
Antiviral drugs, 237–249. See also specific drugs.
  limitations of, 237
  targets for, 238–239, *239*
Anuria, defined, 90
  renal failure with, fluid therapy for, 90–91
Anxiolytics, 466–467. See also specific drugs.
  for destructive behavior, 470
Aplastic anemia, cyclosporine for, 358
  due to sulfonamides, 168
Apomorphine, 484t, 486, 735t
Appetite stimulants, 482–483
  for chronic renal failure, 538
Aprindine, 735t
Aprotinin, 735t
  for acute pancreatitis, 511
Ara C (cytarabine, cytosine arabinoside), 342–343, 741t
Arachidonic acid, biosynthesis of, *667*
  cats' requirement for, 667
  in inflammatory response, 282–283, *282, 285*
  in tissue injury, 305, *305*
Area under the concentration curve (AUC), 4–5, *5*
  bioavailability calculation from, *5*, 6
Arginine vasopressin system, in heart failure, 559, *559*
Arrhythmias, 567–568, *568*
  due to cisapride, 496
  due to doxorubicin, 339–340
  in digitalis intoxication, 576–577
  in dilated cardiomyopathy, 582
  in hypertrophic cardiomyopathy, 585
  treatment of, 586–587
  with gastric dilatation/volvulus, 505
Arsenic intoxication, 719t
Arsenicals. See also specific drugs.
  as anthelmintics, 268t, 274–275
  nephrotoxicity of, 49
Arterial pressure, mean, 586
Arthritis, degenerative, 295–297
    disease-modifying agents for, 297–301, *301, 302*
    glucocorticoids for, 324
  feline chronic progressive, 368
  rheumatoid, 367–368
  septic, 181
Arthus reaction, 44, 353
Articular cartilage. See *Cartilage.*
Ascaris suum–induced airway reactivity, cyclosporine for, 358
Ascites, diuretics for, 525
  drug dose calculation in, 27, *28*
  failure of diuretics in, 520
  in chronic liver disease, 510–511
  spironolactone for, 521t, 525
Ascorbic acid, 715t
  dosage for, 484t, 521t, 735t, 767t
  for acetaminophen toxicity, 295, 484t
  for chronic liver disease, 510
  for copper toxicity, 484t
  for osteoarthritis, 301
  iron interaction with, 110
Asparaginase, 345–346, 735t
  thyroid effects of, 54t
Aspergillosis, 223t, 234
  nasal, 615
Aspiration pneumonia, 620
Aspirin (acetylsalicylic acid), 289–290
  adverse effects of, 287t, 290

Aspirin (acetylsalicylic acid) *(Continued)*
  as antithrombotic, 123
    in heartworm disease, 112t, 123, 595, 596, 611
  dosage for, 112t, 284t, 562t, 733t, 735t
  for glomerular disease, 541
  for hypertrophic cardiomyopathy, 585
  for osteoarthritis, 297
  gastrointestinal disease due to, 50
  hepatotoxicity of, 47
  hypersensitivity to, leukotrienes and, 285
  intoxication with, 719t
  ototoxicity of, 52
  pharmacokinetics of, in cat, 36, 290
    in dog, 290
  pharmacologic effects of, 287
  platelet inhibition by, 56, 288
  selectivity of, for cyclooxygenase isoforms, 284
  spironolactone interaction with, 523
  therapeutic monitoring data for, 63t
  thyroid effects of, 54t
  warfarin therapy with, 122
Association of Feed Company Organizations, nutraceutical marketing guidelines of, 299
Astemizole, 665t, 666, 735t
Asthma, in cats, 617–618
    glucocorticoids for, 323–324
    pathogenesis of, 605
Astringents, as vehicles for topical drugs, 657
  for hemostasis, 116, *116*
Asystole, cardiac, 593
Atenolol, as antiarrhythmic, 562t, 572
  dosage for, 534t, 562t, 735t
  for hypertension, in chronic renal failure, 534t, 539
  for hypertrophic cardiomyopathy, 584, 585
  for mitral valve insufficiency, 581
  structure of, *564*
Atipamezole, 427, 735t
Atopy, 353
  biologic response modifiers for, 673
  fatty acid supplements for, 672
  glucocorticoids for, 323
  treatment of, 365
Atovaquone, 735t
Atracurium besylate, 475
  constant IV infusion rate for, 769t
  dosage for, 474t, 735t
Atrial fibrillation, 586–587
Atrial natriuretic factor, 516
  in heart failure, 559
  in sodium regulation, 76
Atrioventricular nodal block, 587
Atropine, as antiarrhythmic, 562t, 573
  as antiemetic, 484t, *487*
  as bronchodilator, *604*, 608t, 610
  as preanesthetic medication, 425
  dosage for, 484t, 562t, 608t, 735t
  for digitalis intoxication, 577
  in cardiopulmonary resuscitation, 592, 593
  intoxication with, 719t
  parenteral solutions of, interactions with, 20t
Auranofin, 354t, 359–360, 735t
Aurothioglucose, 354t, 359–360, 735t
  for pemphigus, 366
Aurothiomalate, 748t, 768t
Autoimmune disease, cyclosporine for, 358
  drug-induced, 52
  glucocorticoid therapy in, 322, 323
Autonomic nervous system, tricyclic antidepressants' effects on, 463
Autotransfusion, 104
Azathioprine, 359
  dosage for, 354t, 735t
  for chronic active hepatitis, 510
Azathioprine *(Continued)*
  for inflammatory bowel disease, 368, 508
  for myasthenia gravis, 503
  for pemphigus, 366
  for pruritus, 673
  for systemic lupus erythematosus, 367
Azithromycin, 154t, 170, 735t
  bronchial penetration by, 182
Azodyes, hematologic disorders due to, 56, 56t
Aztreonam, 177t, 735t

B

B lymphocytes, in immune response, 350–351, *351*
Bacillus Calmette-Guérin, 360–361
  intravesicular, for lower urinary tract disease, 549
Bacillus piliformis infection, 506
Bacitracin, 151t, 171
Baclofen, 544t, 735t
Bacteremia, infections associated with, 127t, 202–207
  parvovirus-associated, 506
Bacterial infections, 175–219. See also specific infections.
  anaerobic, 213–217
    antimicrobial selection for, 214–216
  associated with bacteremia, 127t, 202–207
  imidazoles for, 228
  L-form, 207
  of abdomen, 203–205
  of central nervous system, 128t, 175–178
  of external ear, 128t, 199. See also *Otitis externa.*
  of gastrointestinal tract, 200–202, 506–507, 508
    organisms causing, 127t
  of genital tract, 128t, 190–191
  of hepatobiliary system, 127t, 510
  of musculoskeletal system, 128t, 179–181
  of respiratory tract, 182–185, 182t, *183*, 616–617, 619
    organisms causing, 127t
  of skin, 128t, 191–196
  of urinary tract, 185–190, 187t
    diagnosis of, 186–187
    organisms causing, 128t
    prophylaxis of, 189
    recurrent, 186, 188–189
    treatment of, 187–189, 187t
  organisms causing, 127t–128t
  prophylaxis of, 217–219
Bacterial overgrowth, 202, 507
  in exocrine pancreatic insufficiency, 512
  in inflammatory bowel disease, 508
  metronidazole for, 485t, 507
Bacteriophages, 387
Bacteriuria, 185
Bacteroides species, antimicrobial resistance in, 215
Bainbridge, quoted, 330
BAL (dimercaprol), 354t, 744t
  for gold chelation, 360
Balantidium coli infection, 508
Baquiloprim-sulfa, 736t
Barbiturates. See also specific drugs.
  adrenocortical effects of, 54t
  for anesthesia induction, 427
  for bacterial meningitis, 178
  for head trauma, 452
  in pediatric animal, 34
  intoxication with, 719t
  thyroid effects of, 54t
Barium, intoxication with, 719t
Barking, excessive, 469–470
BCNU (carmustine), 338, 738t
Beagles, drug disposition in, 37
Beclomethasone, 322, 608t, 736t
  adrenocortical effects of, 54t
Behavioral disorders, in cats, 471–472
  in dogs, 469–471
  neurotransmitters in, 457–458, *458*
  treatment of, 468–472. See also *Behavior-modifying drugs;* specific drugs and classes of drugs.
Behavioral manipulations, in pain control, 407
Behavior-modifying drugs, 457–472, 459t. See also specific drugs and classes of drugs.
  clinical applications of, 468–472
  for pruritus, 672
  for skin diseases, 665t, 668
  structures of, *460*
Belladonna alkaloids. See also specific drugs.
  as antiemetics, 486
  as spasmolytics, 497
  intoxication with, 719t
Benazepril, 562t, 565, 566, 736t
Benzalkonium chloride, 254
  ototoxicity of, 52
  topical preparations of, 658t
Benzathine penicillin, 155t, 157, 761t. See also *Penicillin(s).*
Benzethonium, ototoxicity of, 52
Benzimidazoles, 736t. See also specific drugs.
  as anthelmintics, 268t, 269t, 270–272
Benzocaine, 736t
  hematologic disorders due to, 56, 56t
Benzodiazepines. See also specific drugs.
  as anticonvulsants, 444–446
  as anxiolytics, 466–467
  as appetite stimulants, 482
  as preanesthetic medications, 426
  for aggression, problems with, 467, 469
  for noise phobias, 470
  for pain, 418
  for separation anxiety, 470
  hepatotoxicity of, 466
  in pediatric animal, 34
  mechanism of action of, 444
  neuromuscular blockers' interactions with, 476t
  therapeutic monitoring data for, 63t
  withdrawal from, 466
Benzoyl peroxide, 736t
  as antimicrobial, 659t, 661–662
  as antiseborrheic, 658t, 659
  for canine seborrhea, 673
  for *Malassezia* infection, 233
  for pruritus, 670
Benzyl alcohol, central nervous system toxicity of, 51, 51t
  topical preparations of, 658t
β agonists. See *β-Adrenergic agonists.*
Beta blockers. See *β-Adrenergic blockers.*
β-lactam antibiotics. See *β-Lactam antibiotics.*
Betamethasone, 317t, 322, 736t
  topical preparations of, 658t
Bethanechol, 736t
  as prokinetic agent, 494, *494*
  for hypocontractile bladder, 542, 543t, 544
Bicarbonate. See also *Sodium bicarbonate.*
  in cardiopulmonary resuscitation, 592
  parenteral solutions of, interactions with, 20t
Bicarbonate deficit, calculation of, 88, 531
Bicarbonate–carbonic acid system, 77–78
Bifonazole, 674
Biguanidines. See also specific drugs.
  for diabetes mellitus, 644
Bile acids/salts, 501, 503. See also specific agents.
  hepatotoxicity of, 47

Biliary excretion of drugs, 10–11, *12*
  pathologic factors affecting, 27
Biliary system, organisms causing infections of, 127t
Bioavailability, 6–7
  calculation of, from plasma concentration vs. time curves, *5*, *6*
  changes in, in liver disease, 27
Biofilms, resistance to disinfection and, 255
Biologic response modifiers, 349–380. See also specific agents.
  classification of, 353
  defined, 371
  dosing regimens for, 354t
  for pruritus, 673
  for skin diseases, 669
  immunostimulant, 353, 360–364
  immunosuppressant, 355–360
    for glomerular disease, 541
    indications for, 355
    principles of therapy with, 355
    with renal transplantation, 543
  in neoplasia, 354
  in viral disease, 353–354
  indications for, 353
  recombinant, 392t, 395–396
Bioreversible derivatization, of protein and peptide drugs, 390
Biotechnology, 383–384. See also *Recombinant technology.*
Biotin, 714t
Bipyridines. See also specific drugs.
  for cardiac disease, 577–578
Birds, depolarizing neuromuscular blockers' effects in, 474
Bisacodyl, 484t, 501, 736t
Bismuth, 736t
  central nervous system toxicity of, 51t
  intoxication with, 719t
Bismuth subsalicylate, dosage for, 484t
  for bacterial enteritis, 507
  for diarrhea, 499, 505
  for gastritis, 504
  for *Helicobacter* infection, 505
Bladder, hypercontractile, 543t, 544
  hypocontractile, 542, 543t, 544
Blastomycosis, 223t, 233
Bleach. See *Sodium hypochlorite (bleach).*
Bleomycin, 341, 736t
Blood, 97–105. See also *Blood components;* specific components.
  as immunostimulant, 362
  clinical use of, 101–104, *102*, 102t, *103*
  collection of, 99–100, *99*
  donors of, 98–99, 99t
  drugs acting on, 107–123
  for acute pancreatitis, 511
  for head trauma, 452
  for hemostasis, 116–117
  infections of, 127t, 202–207
  loss of, during surgery, correction for, 94
    shock due to, 590t, 591
  storage of, 100–101, *101*, 102t
    physiologic changes during, 100
  substitutes for, 105
Blood banking services, commercial, 99, 99t
Blood components. See also *Blood;* specific components.
  as immunostimulants, 362
  for hemostasis, 116–117
  storage of, 100–101, *101*, 102t
Blood flow, cutaneous, 654
  hepatic, changes in, in cardiac disease, 28
      in liver disease, 26–27, 27t
    limitation of drug metabolism by, 10, 26
  renal. See *Renal blood flow.*
Blood gas analysis, for acid-base evaluation, 82
Blood groups, 97–98
Blood pressure measurement, 586
Blood typing, laboratories performing, 98
Blood volume, species and breed differences in, drug distribution differences and, 35
Blood-brain barrier, 176
  antimicrobial therapy and, 142t, 143
  meningitis treatment and, 177
  permeability of, after cranial trauma, 421
    in neonate, 32
Body composition, in geriatric animal, 30
Body surface area, conversion of body weight to, 708t
  dosing based on, 16
    for anticancer drugs, 333–334, 333t
Bone, drug movement into, 179–180
  glucocorticoids' effects on, 319, 326
Bone cement, osteomyelitis and, 180
Bone marrow, suppression of. See *Myelosuppression; Neutropenia.*
  transplantation of, 105
Borates, ingestion of, 720t
Bordetella bronchiseptica tracheobronchitis, 183, 246, 616
Botulism, 217, 720t
Boxers, dilated cardiomyopathy in, 582
Brachycephalic breeds, drug disposition in, 37
Bradyarrhythmias, 587
  life-threatening, 593
Brain. See *Central nervous system.*
Bran, 736t
Breed differences, in dilated cardiomyopathy manifestations, 582
  in drug disposition, 35–36
  in response to pain, 407
  in target tissues, 37, *37*
Bretylium, 562t, 572
  constant IV infusion rate for, 769t
  for ventricular fibrillation, 593
Brewer's yeast, 736t
Brodifacoum rodenticide poisoning, 117
Bromethalin, intoxication with, 720t
Bromides, 736t
  as anticonvulsants, 446–448, *446*
    dose modification with, 437, *438*
    for chronic seizure control, 439, 447–448
  intoxication with, 720t
    thiazides for, 523
  pharmacokinetics of, 435t, 447
  skin lesions due to, 53, 53t, 447
  therapeutic monitoring of, 448
    artifacts in, 72, 72t
    data for, 63t
Bromocriptine, 626t, 681, 736t
  for estrus induction, 679, 683
  for hyperadrenocorticism, 626t, 647–648
  thyroid effects of, 54t
Bronchial diseases, 616–618. See also specific diseases.
Bronchial smooth muscle, control of tone of, 602–603, *603*
  heparin's effects on proliferation of, 119
Bronchial-alveolar-blood barrier, 182
Bronchiectasis, 618
Bronchitis, allergic, 365, 618
  in cats, 617
  in dogs, 618
Bronchodilators, 606–610, 608t. See also specific drugs.
  as antitussives, 612
  for bronchial disease, 617, 618
  to facilitate aerosol drug delivery, 615
  ventilation-perfusion mismatch due to, 619
  with antimicrobial therapy for bacterial pneumonia, 184
Bropirimine (ABPP), 364
Brucellosis, 207–208
Brucine, intoxication with, 725t
Buffer, in commercial fluids, 85t
Buffering, in acid-base maintenance, 77
Bulk flow, drug movement by, 6
Bullous pemphigoid, 366
Bunamidine, 736t
Bupivacaine, 413t, 419, 736t
  epidural administration of, 422
  in critically ill animals, 420–421
Buprenorphine, 416–417
  dosage for, 413t, 426t, 736t
  parenteral solutions of, interactions with, 20t
  pharmacokinetics of, 410
  receptor selectivity of, 409t
  safety of, after cranial trauma, 422
Burow's solution, 657
Buspirone, 459t, 467, 736t
  for destructive behavior, 470
  for inappropriate elimination in cats, 471
  for phobias, 470
Busulfan, 736t
Butamisole, 736t
Butorphanol, 416
  as antiemetic, 411
    with cancer chemotherapy, 335
    with cisplatin, 344
    with nitrosoureas, 338
  as antitussive, 608t, 612
  constant IV infusion rate for, 769t
  dosage for, 413t, 426t, 608t, 736t
  parenteral solutions of, interactions with, 20t
  pharmacokinetics of, 410
  receptor selectivity of, 409t
  structure of, *409*
N-Butyl chloride, 268t, 269t, 275
Butyrophenones, 460. See also specific drugs.
  as antiemetics, 487
  central nervous system toxicity of, 51t, 439

C

Cabergoline, 681
  for estrus induction, 679
  for pregnancy termination, 687
Caffeine, intoxication with, 720t
Calcifediol, *633*, 634
  for hypoparathyroidism, 634
Calcitonin, 736t
  for hypercalcemia, 94, 635
Calcitriol, *633*, 634
  dosage for, 534t, 626t, 736t, 768t
  for hyperparathyroidism, in chronic renal failure, 534t, 539–540
  for hypoparathyroidism, 626t, 634
Calcium, as inotrope, 579
  for hyperkalemia in hypoadrenocorticism, 649
  for hypoparathyroidism, 633–634
  in cardiac muscle action potential, 555, 556, *556*
  in cardiopulmonary resuscitation, 592, 593
  in commercial fluids, 85t
  in myocardial contractility regulation, 553–554, *554*
  in vascular smooth muscle contractility, 556–557, *557*
  parenteral solutions containing, interactions with, 20t
  regulation of, glucocorticoids' effects on, 316
    parathyroid gland in, 632, *633*
Calcium acetate, dosage for, 534t
  for chronic renal failure, 534t, 536
Calcium carbonate, as antacid, 492

- Calcium carbonate *(Continued)*
  - dosage for, 484t, 534t, 736t
  - for chronic renal failure, 534t, 536
  - for hypoparathyroidism, 634
  - in bone, as acid buffer, 77
- Calcium channel blockers, 561–565. See also specific drugs.
  - adverse effects of, 564
  - as antiarrhythmics, 572–573
  - clinical use of, 564–565
  - drug interactions with, 564
    - digoxin, 564, 575
  - for hypertension in chronic renal failure, 539
  - for respiratory disease, 610
  - mechanisms of action of, 561
  - pharmacokinetics of, 561–564
- Calcium chloride, 736t
  - constant IV infusion rate for, 769t
  - for hypocalcemia, 94
  - for hypoparathyroidism, 634
  - in cardiopulmonary resuscitation, 592
- Calcium citrate, 736t
- Calcium disodium EDTA, 737t, 743t
  - parenteral solutions of, interactions with, 20t
- Calcium glucoheptonate, for hypoparathyroidism, 634
- Calcium gluconate, constant IV infusion rate for, 769t
  - dosage for, 530t, 626t, 737t
  - for hyperkalemia, 87, 87t, 626t
    - in acute renal failure, 530t, 531
  - for hypocalcemia, 94
  - for hypoparathyroidism, 626t, 634
- Calcium lactate, 737t
  - for hypoparathyroidism, 634
- Calcium oxalate urolithiasis, 526
  - hydrochlorothiazide for, 521t
- Calcium phosphate, in bone, as acid buffer, 77
- Calculi, urinary. See *Urolithiasis.*
- Calicivirus infection, in cats, 238t, 247
- *Campylobacter jejuni* enteritis, 506
- Cancer. See also *Neoplasia.*
  - classification of, by treatment sensitivity, 332
  - doubling times for, 331
  - hepatocellular, due to anabolic steroids, 114
  - hypercalcemia in, 635
  - interferons for, 375
  - mammary gland, 682t, 687
  - pathogenesis of, 43
  - prostatic, 687
- Candidiasis, 223t, 233
- Capacity-limited drugs, 10, 26
  - hepatic disease's effects on, 27, 27t
  - in geriatric animal, 29
- *Capillaria aerophila* infection, 619
- Capillaries, types of, drug movement and, 142
- Captan, 231, 232t, 737t
- Captopril, 562t, 565, 737t
- Carbamates, topical, as antiparasitics, 663
- Carbamazepine, dosage for, 459t, 737t
  - for aggression, 467, 469
  - for behavioral modification, 467
  - for diabetes insipidus, 651
  - neuromuscular blockers' interactions with, 476t
  - thyroid effects of, 54t
- Carbamide peroxide, 661
  - for otitis externa, 197
- Carbapenem, structure of, *153*
- Carbaryl, for ear mites, 199
  - topical, 658t
- Carbenicillin, 156
  - dosage for, 154t, 737t
  - for urinary tract infections, 187t
  - parenteral solutions of, interactions with, 20t
- Carbenicillin *(Continued)*
  - pharmacokinetics of, 157
  - susceptibility test interpretation for, 134t
- Carbenoxolone, for urinary tract infection, 186
- Carbimazole, 737t
  - for hyperthyroidism, 630
- Carbohydrate metabolism, 636
  - glucocorticoids and, 315–316, 327, 328, 641
  - tests of, 626t, 637
- Carbolic acid, 254
- Carbon dioxide, serum total, for acid-base evaluation, 82
- Carbon monoxide, intoxication with, 720t
- Carbon tetrachloride, intoxication with, 720t
- Carbonic anhydrase inhibitors, *516*, 519t, 520–522
- Carboplatin, 344–345, 737t
- Carcinogenesis, 43
- Carcinoma. See also *Cancer; Neoplasia.*
  - hepatocellular, due to anabolic steroids, 114
  - mammary gland, 682t, 687
  - prostatic, 687
- Cardiac asystole, 593
- Cardiac disease. See also *Heart failure;* specific diseases.
  - changes in drug disposition in, 27–28, 28t
- Cardiac glycosides. See *Digitalis glycosides; Digitoxin; Digoxin.*
- Cardiac muscle, action potential of, 555–556, *556*
- Cardiogenic shock, 89, 588
- Cardiomyopathy, 581–585
  - dilated, in cats, 583–584
    - in dogs, 581–583
  - hypertrophic, 584–585
    - negative chronotropes for, 579
  - in hyperthyroidism, 585, 629–630
    - treatment of, 631
  - restrictive, 585
- Cardiopulmonary cerebrovascular resuscitation, 591–593
- Cardiotoxicity, of cisapride, 496
  - of doxorubicin, 339–340
- Cardiovascular system, 553–598
  - diseases of. See also specific diseases.
    - drugs used in, 562t–563t
    - treatment of, 579–588
  - glucocorticoids' effects on, 318, 327
  - in geriatric animal, 29
  - physiology of, 553–558, *554, 556–558*
  - tricyclic antidepressants' effects on, 463
- Carmustine (BCNU), 338, 737t
- Carnitine, 737t
  - deficiency of, in dilated cardiomyopathy in dogs, 581–582
- Carprofen, 290–292, 737t
  - adverse effects of, 287t, 291
  - for osteoarthritis, 297
  - for thoracolumbar disc extrusion, 454
  - selectivity of, for cyclooxygenase isoforms, 284, 291
- Cartilage, articular, fluorinated quinolones' effects on, 166
  - glucocorticoids' effects on, 319
  - in osteoarthritis, 296
  - normal physiology of, 296, *298*
  - NSAIDs' effects on, 286
- Carvedilol, 571–572
- Cascara sagrada, 737t
- Castor oil, 501, 737t
- Castration, changes in gonadotropins after, 678–679
- Catecholamines. See also specific catecholamines.
  - in heart failure, 560
- Cathartics, 499–501
- Catheter, central venous, for drug delivery in cardiopulmonary resuscitation, 592
- Catheterization, urinary tract infection and, 186
- Caustics, therapeutic use of, 661
- CCNU (lomustine), 338, 750t
- Cefaclor, 154t, 156, 737t
  - for urinary tract infections, 187t
  - susceptibility test interpretation for, 134t
- Cefadroxil, 152t, 157
  - dosage for, 154t, 737t
  - for pyoderma, 194
  - for urinary tract infections, 187t
  - susceptibility test interpretation for, 134t
- Cefamandole, 154t, 156, 737t
  - susceptibility test interpretation for, 134t
- Cefazolin, 152t, 156
  - bone penetration by, 180, 181t
  - central nervous system toxicity of, 51, 51t
  - dosage for, 154t, 737t
  - for osteomyelitis, 181t
  - for surgical prophylaxis, 219
  - minimum inhibitory concentrations for selected organisms for, 132t
  - parenteral solutions of, interactions with, 20t
  - susceptibility test interpretation for, 134t
- Cefepime, 154t, 737t
- Cefixime, 154t, 737t
- Cefmetazole, 154t, 737t
- Cefoperazone, 154t, 156, 157, 737t
- Cefotaxime, 152t, 156, 157
  - bronchial penetration by, 182, 182t
  - dosage for, 154t, 177t, 737t
  - minimum inhibitory concentrations for selected organisms for, 132t
  - susceptibility test interpretation for, 134t
- Cefotetan, 154t, 737t
  - susceptibility test interpretation for, 134t
- Cefoxitin, 158
  - bronchial penetration by, 182, 182t
  - dosage for, 154t, 737t
  - efficacy of, pH and, 140
  - for anaerobic infections, 216
  - for peritonitis, 204
  - for surgical prophylaxis, 219
  - minimum inhibitory concentrations for selected organisms for, 132t
  - resistance to, in *Bacteroides fragilis,* 215
  - spectrum of activity of, 152t, 156
  - susceptibility test interpretation for, 134t
- Cefpodoxime, 154t, 737t
- Ceftazidime, 156
  - dosage for, 154t, 177t, 737t
  - for chemotherapy-related infection, 335
  - susceptibility test interpretation for, 134t
- Ceftiofur, 152t, 156, 157
  - dosage for, 154t, 737t
  - for canine parvoviral enteritis, 245
  - minimum inhibitory concentrations for selected organisms for, 132t
  - susceptibility test interpretation for, 134t
- Ceftizoxime, 154t, 737t
  - susceptibility test interpretation for, 134t
- Ceftriaxone, 157
  - aerosol therapy with, 615t
  - dosage for, 154t, 177t, 737t
  - susceptibility test interpretation for, 134t
- Cefuroxime, 154t, 737t
  - susceptibility test interpretation for, 134t
- Cell cycle, 330–331, *330*
- Cell wall, bacterial, antimicrobial penetration of, *129*, 143
  - antimicrobials targeting, 141, *141*, 150–153, *152, 153*
- Cellulose, oxidized, as clotting matrix, 116, *116*
- Center for Veterinary Medicine, 693, 694, 694t

Center for Veterinary Medicine *(Continued)*
  adverse drug reaction reporting to, 57–58, 699–701
Central nervous system, bacterial infections of, 128t, 175–178
  disease of, drug-induced. See *Central nervous system toxicity.*
    glucocorticoids for, 324
  disturbances of, in acute renal failure, 532
  glucocorticoids' effects on, 319
  in geriatric animal, 29
  trauma to, causes of, 450–451
    glucocorticoids for, 324
    inflammatory response modifiers for, 304–307
    medical management of, 451–453
    pain control in, 421–422
    pathophysiology of, 450
Central nervous system toxicity, 50–51, 51t
  in cardiac disease, 28
  in pediatric animal, 32
  of 5-fluorouracil, 343
  of glucocorticoids, 51t, 326
  of lidocaine, 51t, 439, 570, 571
  of metoclopramide, 51t, 495
  of mitotane, 647
  of opioids, 51t, 410–412
Central sensitization to pain, 406
Central venous catheter, for drug delivery, in cardiopulmonary resuscitation, 592
Central venous pressure, for fluid therapy monitoring, 85
    in oliguric renal failure, 91
Cephalexin, 156
  bronchial penetration by, 182
  dosage for, 154t, 737t
  for pyoderma, 194
  for urinary tract infections, 187t
  minimum inhibitory concentrations for selected organisms for, 132t
  susceptibility test interpretation for, 134t
Cephaloridine, 737t
  nephrotoxicity of, 49
Cephalosporins, 156. See also *β-Lactam antibiotics;* specific drugs.
  bronchial penetration by, 182
  classification of, 151t, 156
  for anaerobic infections, 216
  for pyoderma, 193
  for urinary tract infections, 187t
  nephrotoxicity of, 49
  parenteral solutions of, interactions with, 20t
  pharmacokinetics of, 157
  structure of, *153*
Cephalothin, 152t, 156, 157
  dosage for, 154t, 737t
  for osteomyelitis, 181t
  minimum inhibitory concentrations for selected organisms for, 132t
  parenteral solutions of, interactions with, 20t
  relative efficacy of, *133*
  susceptibility test interpretation for, 134t
Cephapirin, 154t, 157, 737t
  susceptibility test interpretation for, 134t
Cephradine, 738t
  for urinary tract infections, 187t
  susceptibility test interpretation for, 134t
Cerebral edema, 451
  due to aggressive correction of hypernatremia, 86
  furosemide for, 521t
  glucocorticoids for, 324
  in bacterial meningitis, 176
    anti-inflammatory drugs for, 177–178
  in diabetic ketoacidosis, 642
  mannitol for, 521t
Cerebrospinal fluid, 176
Cerebrovascular cardiopulmonary resuscitation, 591–593
Ceruminolytics, 661
  for otitis externa, 197
Ceruminous otitis, 199–200
Cetacaine, 738t
Cetirizine, 611
Chagas disease, 573
Charcoal, activated, 499
    dosage for, 484t, 733t, 738t
    preparations of, 718t
Chemoreceptor triggering zone, 483, *486, 487*
  antiemetics active at, 487–488, *487*
  stimulation of, to induce emesis, 486
Chemotherapeutic triangle, in antimicrobial therapy, 125, *126*
Chemotherapy, 330–347. See also *Anticancer drugs;* specific drugs and classes of drugs.
  adjuvant, 332
  anabolic steroids and, 115
  combination, 333
  glucocorticoids in, 325–326
  guidelines for, 334
  phases of, 332–333
  resistance to, 332
  side effects of, 334–336
Chenodiol (chenodeoxycholic acid), 503
Chest tube drainage, for pyothorax, 184
Cheyletiellosis, ivermectin for, 665t, 669
Chlorambucil, as anticancer drug, 337–338
  as immunosuppressant, 359
  dosage for, 354t, 738t
  for eosinophilic granuloma, 367
  for feline infectious peritonitis, 247
  for pemphigus, 366–367
Chloramphenicol, 151t, 169–170
  adverse effects of, 170
  aerosol therapy with, 615t
  dosage for, 154t, 177t, 738t
  drug interactions with, calcium channel blockers, 564
    levamisole, 272
    phenobarbital, 64, 170, 434
    phenytoin, 444
    primidone, 442
  for anaerobic infections, 216
  for ehrlichiosis, 212
  for otitis externa, 197t, 199
  for pyoderma, 194
  for urinary tract infections, 187t
  gastrointestinal disease due to, 50
  hematologic disorders due to, 56, 56t
  minimum inhibitory concentrations for selected organisms for, 132t
  parenteral solutions of, interactions with, 20t
  pharmacokinetics of, 169
  seizures due to, 439
  skin lesions due to, *52,* 53, 53t
  spectrum of activity of, 152t, 169
  structure of, *159*
  susceptibility test interpretation for, 134t
Chlordiazepoxide, 466–467
  dosage for, 459t, 738t
  for inappropriate elimination in cats, 471
  for social anxiety in cats, 472
Chlorhexidine, 662
  as germicide, *251,* 252
  dosage for, 232t, 738t
  for dermatophytosis, 231
  for *Malassezia* infection, 233
  for otitis externa, 197, 198t
  for periodontal disease, 200
  for pruritus, 670–671
  for surgical antisepsis, 256
  for wound antisepsis, 256–257
Chlorhexidine *(Continued)*
  ototoxicity of, 52
Chloride, disease-induced changes in, 79
  in extracellular fluid osmolality, 76
  intestinal transport of, 496
  metabolic alkalosis responsive to, 82
  renal transport of, 515–516, *516, 517*
Chlorine, as germicide, 252–253
  in commercial fluids, 85t
Chlorothiazide, 522, 738t
Chloroxylenols, as germicides, 254
  for surgical antisepsis, 256
Chlorpheniramine, dosage for, 608t, 665t, 738t
  for allergic rhinitis, 608t, 614
  for pruritus, 671–672
  for skin disease, 665t, 666
Chlorpromazine, 487
  adverse effects of, 461
  antiarrhythmic effect of, 461
  dosage for, 484t, 738t
  drug interactions with, 461
    neuromuscular blockers, 476t
  for acute gastritis, 504
  for diarrhea, 498
  thyroid effects of, 54t
Chlorpropamide, 626t, 651, 738t
Chlorpyrifos, 663
Chlortetracycline, 169, 738t
Chocolate, intoxication with, 720t
Cholagogues, 501
Cholangiohepatitis, chronic, 510
Cholangitis, chronic, 510
  metronidazole for, 485t
Cholecalciferol, *633,* 738t. See also *Calcitriol; Vitamin D.*
  for hypoparathyroidism, 634
  in rodenticides, hypercalcemia due to, 635
  structure of, *632*
Choleretics, 501
Cholestasis, drug-induced, 45
  ursodeoxycholic acid for, 501
Cholesterol, amphotericin B binding to, 225, *225*
Cholestyramine, 499
  dosage for, 484t, 738t
  for diarrhea in short bowel syndrome, 507
  for digitalis intoxication, 577
  thyroid effects of, 54t
Choline, 501–502
  dosage for, 484t
Cholinergic agents, as prokinetic drugs, 494, *494*
  for hypocontractile bladder, 543–545
  intoxication with, 720t
Cholinergic receptors, in gastric motility, 494, *494*
Cholinesterase inhibitors. See *Anticholinesterases;* specific agents.
Chondrocytes, in articular cartilage, 296, *298*
Chondrodystrophoid breeds, acute thoracolumbar disc extrusion in, 453–454
Chondroitin sulfate, for osteoarthritis, 300–301, *301*
  for septic arthritis, 181
  for urinary tract infection, 189
  in articular cartilage, 296, *298*
Chondroprotectants, 297–301, *301, 302.* See also specific agents.
Chordae tendineae, ruptured, 580, 581
Chorionic gonadotropins, 738t, 746t
  equine, 679, 681
    for estrus induction in cats, 684
  human. See *Human chorionic gonadotropin.*
Chromium, 716t
Chrysotherapy. See *Gold compounds.*
Cilastatin, imipenem with. See *Imipenem-cilastatin.*

- Cilia, in respiratory defense, 603–604, *603*
- Cimetidine, as immunostimulant, 364
  - constant IV infusion rate for, 769t
  - dosage for, 484t, 530t, 534t, 738t
  - drug interactions with, 490
    - anticonvulsants, 434
    - calcium channel blockers, 564
    - diazepam, 479
    - metronidazole, 265
    - sucralfate, 493
  - for acetaminophen toxicity, 36, *46*, 47, 295
  - for acute liver failure, 509
  - for gastrointestinal ulceration, *489*, 490, 491
  - for nausea and vomiting, in acute renal failure, 530t
    - in chronic renal failure, 534t, 538
  - hematologic disorders due to, 56t, 490
  - thyroid effects of, 54t
  - to prevent dapsone toxicity, 666
  - with pancreatic extract, 503
- Ciprofloxacin, bronchial penetration by, 182t
  - dosage for, 154t, 177t, 738t
  - for leptospirosis, 208
  - minimum inhibitory concentrations for selected organisms for, 132t
  - pharmacokinetics of, 165
  - structure-activity relationship of, 163, *163*
  - susceptibility test interpretation for, 134t
  - veterinary use of, 162–163, 166, 194
- Circadian rhythms, species differences in drug disposition and, 37
- Cirrhosis, diuretics for, 525
  - drug-induced, 45
- Cisapride, *494*, 495–496, *495*
  - dosage for, 484t, 738t
  - for gastroesophageal reflux, 504
  - for hypocontractile bladder, 545
- Cisplatin, 344, 738t
  - constant IV infusion rate for, 769t
  - furosemide interaction with, 524
  - ototoxicity of, 52
- Citrate phosphate dextrose, for stored blood preservation, 100
- Citrate toxicity, in blood recipient, 104
- *c-kit* ligand. See *Stem cell factor.*
- Clarithromycin, 154t, 738t
  - for *Helicobacter* infection, 505
- Clavulanic acid, bronchial penetration by, 182t
  - β-lactam antibiotics combined with, 156, 157. See also *Amoxicillin-clavulanic acid; Ticarcillin-clavulanic acid.*
- Clearance, drug, 13, *13*
- Clemastine, 665t, 666, 738t
  - for pruritus, 671, 672
- Clindamycin, 170
  - bronchial penetration by, 182, 182t
  - dosage for, 154t, 738t
  - efficacy of, pH and, 140
  - for anaerobic infections, 216
  - for empyema, 621
  - for oral cavity infections, 200
  - for osteomyelitis, 181t
  - for peritonitis, 204
  - for surgical prophylaxis, 219
  - for toxoplasmosis, 263
  - minimum inhibitory concentrations for selected organisms for, 132t
  - neuromuscular blockers' interactions with, 476t
  - spectrum of activity of, 152t, 170, 258t
  - structure of, *159*
  - susceptibility test interpretation for, 134t
- Clinical trials, ethical considerations in, 702–704
  - in human drug approval process, 694–695
  - reporting and reviewing, 704–705
- Clobetasol, 658t
- Clofazimine, 210
  - dosage for, 154t, 665t, 738t
- Clofibrate, 651
- Clomiphene, 680, 739t
- Clomipramine, 462, 464
  - accumulation of, 463
  - adverse effects of, 463, 464
  - dosage for, 459t, 665t, 739t
  - drug interactions with, 464
  - for acral lick dermatitis, 469, 673
  - for dominance-related aggression, 469
  - for inappropriate elimination in cats, 471
  - for interdog aggression, 469
  - for skin diseases, 665t, 668
- Clonazepam, *433*
  - as anticonvulsant, 446
  - as anxiolytic, 466, 467
  - dosage for, 459t, 739t
  - for acute seizure management, 437
- Clonidine, adrenocortical effects of, 54t
  - for diarrhea, 498
  - for opioid withdrawal, 412
  - transdermal administration of, 670
- Clonidine stimulation test, for growth hormone deficiency, 626t, 650
- Clorazepate, *434*, 444–446
  - as anxiolytic, 466
  - dosage for, 435t, 459t, 739t
  - for inappropriate elimination in cats, 471
  - for noise phobias, 470
  - pharmacokinetics of, 434, 445
  - phenobarbital interaction with, 434, 445, 446, 466
- *Clostridium botulinum*, 217, 720t
- *Clostridium difficile* enteritis, 506
  - clindamycin therapy and, 216
- *Clostridium perfringens*, enteritis due to, 217, 506, 508
  - overgrowth of, in inflammatory bowel disease, 508
- *Clostridium tetani* infection, 216–217
  - muscle relaxants for, 480
- *Clostridium tetani* toxoid, 770t
- Clotrimazole, 228
  - aerosol therapy with, 615t
  - dosage for, 232t, 739t
  - for aspergillosis, 234, 615
  - spectrum of activity of, 223t, 228
  - topical, 662
- Clotting factors, heparin inhibition of, 118–119, *119*
  - stability of, in frozen plasma, 101
  - topical preparations of, 116, *116*
- Cloxacillin, 154t, 155–156, 739t
  - susceptibility test interpretation for, 134t
- Coagulation. See *Hemostasis.*
- Coagulation factors, heparin inhibition of, 118–119, *119*
  - stability of, in frozen plasma, 101
  - topical preparations of, 116, *116*
- Coal tar, 739t
  - as antiseborrheic, 658t, 659
  - as irritant, 661
  - for canine seborrhea, 673
  - skin lesions due to, 53, 53t
- Cobalamin (vitamin B_{12}), 107–108, *108*, 715t
  - dosage for, 112t, 767t
  - for exocrine pancreatic insufficiency, 512
- Cocaine, intoxication with, 720t
- Coccidioidomycosis, 234
  - drug susceptibilities of, 223t
  - intestinal, 507
  - pulmonary, 619
- Coccidiosis, common enteric, 258–261, 258t, *259*
- Cod liver oil, 739t
- Codeine, 416
  - acetaminophen with, 413t, 733t
  - as antitussive, 608t, 611
  - dosage for, 413t, 608t, 739t
  - receptor selectivity of, 409t
  - structure of, *409*
- Coenzyme Q-10, 579, 739t
- Colchicine, 740t
  - for chronic liver disease, 510
  - for renal amyloidosis, 542
- Colibacillosis, neonatal, 202
- Colistin, 171, 197t
- Colitis, hemorrhagic, due to *Bacillus piliformis*, 506
    - due to doxorubicin, 335
  - nervous, 507–508
  - ulcerative. See *Inflammatory bowel disease.*
- Collars, for antiparasitic drug delivery, 662
    - skin lesions due to, 53, 53t
- Collies, ivermectin toxicity in, 50, 597, 598, 669
- Colloidal oatmeal, 658t, 670
- Colloidal solutions, 84, 84t. See also *Fluid therapy.*
  - for head trauma, 452
  - for shock, 590t
- Colonization, infection vs., 129, 130
    - in external ear, 196
    - in skin, 191
- Colostrum absorption, intestinal permeability before, 31
- Compassionate use, 696, 698
- Complement, in immune response, 351
  - in immune-mediated hemolytic anemia, 365
  - in inflammatory response, *282*, 283t
- Compound A, 430
- Compounding, guidelines on, 698
- Conduction velocity, 556
- Conjugation, in drug metabolism, 10
    - species differences in, 36
- Conjunctiva, normal flora of, 128t
  - organisms causing infections of, 128t
- Consciousness, levels of, in pain control, 407
- Consent, informed, 703–704
- Contact dermatitis, allergic, 368
- Convulsions. See *Seizures.*
- Cooling, for hyperthermia, 588
- Copper, 716t
  - intoxication with, 509–510, 720t
    - ascorbic acid for, 484t
- Corn oil, for canine seborrhea, 673
- Corneal ulceration, ophthalmic glucocorticoids and, 326, 328
- Coronavirus, feline infectious peritonitis due to, 238t, 246–247
- Corticosteroids. See *Glucocorticoid(s); Mineralocorticoids;* specific agents.
- Corticosterone, feedback regulation of, 313–314, *314*
- Corticotropin (ACTH), 313–314, *314*
  - measurement of, in hyperadrenocorticism diagnosis, 646
    - in hypoadrenocorticism diagnosis, 648
  - normal concentrations of, 625t
  - provocative testing with, 740t
    - in hyperadrenocorticism diagnosis, 626t, 645–646
    - in hypoadrenocorticism diagnosis, 648
- Corticotropin-releasing factor, 313, *314*
- Cortisol, feedback regulation of, 313–314
  - measurement of, in hyperadrenocorticism diagnosis, 645–646
  - normal concentrations of, 625t
  - phenytoin interaction with, 444
- Cortisone, 315, 739t

Cortisone *(Continued)*
  adrenocortical effects of, 54t
Cosequin, 739t
  for osteoarthritis, 301, *302*
  for septic arthritis, 181
Cosyntropin, 739t. See also *Corticotropin (ACTH).*
Cough, kennel, 183, 238t, 246, 616–617
  suppression of, 608t, 611–612
    by opioids, 411, 611–612
  with bronchial disease, 618
  with tracheal collapse, 616
  with tracheitis, 616
Cough reflex, 603, 611, *612*
Coumarin derivatives. See also *Dicumarol; Warfarin.*
  as anticoagulants, 121–122
  hematologic disorders due to, 56t
  intoxication with, 720t
    vitamin K for, 117
COX enzymes (cyclooxygenases), glucocorticoids' effects on, 317, *317*
  in inflammatory response, 283
  inhibition of, by NSAIDs, 283–284, *285*
Cranberry juice, for urinary tract infection, 189
Cranial trauma. See *Central nervous system, trauma to.*
"Crash cart" drugs, 592–593
Crayons, intoxication with, 720t
Creams, 656
Creatinine, serum, dose adjustment using, in renal disease, 26
Creatinine clearance, dose adjustment using, in renal disease, 26
Critical illness, pain control in, 420–421
Crohn's disease. See *Inflammatory bowel disease.*
Cromolyn, 610, 739t
Crossmatching, 98
Cryoprecipitate, indications for, 104
  preparation and storage of, 101, 102t
Cryptococcosis, 223t, 233–234
  pulmonary, 619
Cryptorchidism, 682t, 687
Cryptosporidiosis, 507
Crystalloid solutions, 83–84, 84t. See also *Fluid therapy.*
  for cardiopulmonary resuscitation, 592
  for head trauma, 452
  for shock, 590t
Culture and susceptibility testing, 130–139
  dose calculation from, 137–138, *138*
  for anaerobes, 214
  for fungal infections, 223, 223t
  interpretation of, 131–137, 132t, *133*, 134t–135t
  methods for, 130–131, *130*, *131*
    automated, 137
  repetitive, in evaluating response to therapy, 148
Curare, intoxication with, 721t
Cushing's syndrome. See *Hyperadrenocorticism.*
Cyanide, intoxication with, 721t
Cyanocobalamin (vitamin B_{12}), 107–108, *108*, 715t
  dosage for, 112t, 739t, 767t
  for exocrine pancreatic insufficiency, 512
Cyclic adenosine monophosphate, in control of airway caliber, 602, *603*
  in myocardial contractility, *554*, 555
  in vascular smooth muscle contractility, 557, *557*
Cyclic guanosine monophosphate, in control of airway caliber, 602, *603*
  in vascular smooth muscle contractility, 557, *557*
Cyclizine, 484t, 486, 739t
Cyclooxygenases, glucocorticoids' effects on, 317, *317*
  in inflammatory response, 283
  inhibition of, by NSAIDs, 283–284, *285*
Cyclophosphamide, antidiuretic hormone secretion and, 526
  as immunosuppressant, 359
  dosage for, 354t, 739t
  for cancer, 336–337
  for feline infectious peritonitis, 247
  for immune-mediated hemolytic anemia, 365
  for pemphigus, 366
  for pulmonary granulomatosis, 620
  for systemic lupus erythematosus, 367
Cyclosporine, 355–358
  adverse effects of, 356–357
  as immunosuppressant with renal transplantation, 543
  dosage for, 354t, 740t
  drug interactions with, 356
    calcium channel blockers, 564
  for immune-mediated hemolytic anemia, 365
  for inflammatory bowel disease, 368
    with dexamethasone, 358
  ketoconazole with, 356
    cost analysis of, 357–358
  mechanism of action of, 355–356
  pharmacokinetics of, 356
  structure of, 355, *355*
  therapeutic monitoring of, 63t, 357
Cyclothiazide, 740t
Cyproheptadine, as antiemetic, 488
  as appetite stimulant, 483
  dosage for, 484t, 626t, 665t, 740t
  for hyperadrenocorticism, 626t, 647
  for respiratory disease, 611
Cystine urolithiasis, penicillamine for, 521t
  urine acidity and, 526
Cystitis, 185. See also *Urinary tract infections.*
  feline interstitial, 547–548
  hemorrhagic, due to cyclophosphamide, 337
Cysts, ovarian follicular, 682t, 684–685
Cytarabine (cytosine arabinoside), 342–343, 740t
Cythioate, 663, 668, 740t
Cytochrome P450 enzymes, 10. See also *Enzymes, drug-metabolizing.*
  thyroid disease's effects on, 28
Cytokines, 371–372. See also specific cytokines.
  cloned canine and feline, 372t
  in immune response, 349, 350t
  in septic shock pathogenesis, 304
  inhibitors of, 372
  nomenclature of, 371
  receptors for, 372
  recombinant human, 392t, 396
    commercially available, 372t
Cytosine arabinoside (cytarabine), 342–343, 740t
Cytotoxic adverse drug reactions, 41, *42*
Cytotoxic drugs. See *Anticancer drugs; Chemotherapy;* specific drugs.
Cytotoxic hypersensitivity reaction, 44, 352–353
  treatment of, 365–367
Cytotoxicity, antibody-dependent cell-mediated (ADCC), 351
  cell-mediated, 350, 351
Cytotoxins, gastrointestinal disease due to, 202

D

Dacarbazine, 338, 740t
Dactinomycin (actinomycin D), 341, 733t, 740t
Dakin's solution, 253. See also *Sodium hypochlorite (bleach).*
  for wound antisepsis, 257
Danazol, 359
  adrenocortical effects of, 54t
  dosage for, 112t, 354t, 740t
  for immune-mediated hemolytic anemia, 365
  for thrombocytopenia, 115
Danthron, dosage for, 484t
Dantrolene, 480
  dosage for, 543t, 740t
  for feline urologic syndrome, 548
  for hypertonic urethra, 546
  for tetanus, 217
  neuromuscular blockers' interactions with, 476t
Dapsone, 196, 665–666
  dosage for, 154t, 232t, 665t, 740t
  for leprosy, 196, 210
  for rhinosporidiosis, 232t, 234
Darbazine, 740t
DDAVP (desmopressin), 650
  dosage for, 112t, 626t, 740t
  for diabetes insipidus, 626t, 651
  for hemostasis, 117–118
  provocative testing with, in diabetes insipidus diagnosis, 651
DDT (dichlorodiphenyltrichloroethane), phenytoin interaction with, 444
Decongestants, 608t, 614
  intoxication with, 721t
Decoquinate, 740t
Defecation, inappropriate, in cats, 471
Deferoxamine mesylate, 740t
  for shock, 590t
Degenerative joint disease, 295–297
  disease-modifying agents for, 297–301, *301*, *302*
  glucocorticoids for, 324
Dehydration, determining degree of, 83, 83t
  due to osmotic diuretic, 520
Dehydrocholic acid, 484t, 740t
  for chronic liver disease, 510
  for digestive disorders, 503
Delta-Albaplex, 740t
Demeclocycline, 740t
Demodectic mange, generalized, 674
  ivermectin for, 665t
  milbemycin for, 665t, 669
Demulcents, as vehicles for topical drugs, 657
Dental procedures, antibiotic prophylaxis for, 200
Deoxycholic acid, hepatotoxicity of, 47
Deoxycorticosterone, adrenocortical effects of, 54t
Deoxycorticosterone acetate, 740t
  for hypoadrenocorticism, 626t, 649
Deoxycorticosterone pivalate, 322
  dosage for, 626t, 741t
  for hypoadrenocorticism, 626t, 649
Deprenyl. See *Selegiline.*
Dermatitis, acral lick, 469, 673
  allergic contact, 368
  drug-induced, 53
Dermatomyositis, 367
Dermatophytosis, 231–232, 674–675
  topical therapy for, 662
    limitations of, 674
Dermatosis, growth hormone–responsive, 650
  psychogenic, in cats, 472, 672
    in dogs, 470–471
Dermis, 654
Desflurane, 430
Desipramine, 462
Desmopressin (DDAVP), 650
  dosage for, 112t, 626t, 740t

- Desmopressin (DDAVP) *(Continued)*
  - for diabetes insipidus, 626t, 651
  - for hemostasis, 117–118
  - provocative testing with, in diabetes insipidus diagnosis, 651
- Desonide, 658t
- Desoximetasone, 658t
- Desoxycorticosterone acetate, 741t
  - for hypoadrenocorticism, 626t, 649
- Desoxycorticosterone pivalate, 322
  - dosage for, 626t, 741t
  - for hypoadrenocorticism, 626t, 649
- Destructive behavior, 470
- Detergents, intoxication with, 721t
- Detrusor instability, 544t, 545
- Dexamethasone, 317t, *320*, 321
  - adrenocortical effects of, 54t
  - as antiemetic, 488
  - dosage for, 354t, 562t, 608t, 665t, 741t
  - for bacterial meningitis, 177–178
  - for cancer, 346–347
  - for central nervous system trauma, 324
  - for hemorrhagic shock, 306, 325
  - for immune-mediated hemolytic anemia, 326, 365
  - for immune-mediated thrombocytopenia, 326
  - for inflammatory bowel disease, 324–325, 508
    - cyclosporine with, 358
  - for septic shock, 306, 325
  - for thoracolumbar disc extrusion, 453–454
  - phenytoin interaction with, 444
- Dexamethasone suppression test, in hyperadrenocorticism diagnosis, 646
- Dexpanthenol, 741t
- Dexrazoxane, 741t
  - as cardioprotectant with doxorubicin, 340
- Dextran, 84, 741t
  - constant IV infusion rate for, 769t
  - for shock, 590t
- Dextroamphetamine, 468, 741t
  - for hyperactivity, 471
- Dextrometamphetamine, dosage for, 459t
- Dextromethorphan, 608t, 612, 741t
- Dextrose, 741t
  - for hyperkalemia, in acute renal failure, 530t, 531
  - for hypoglycemia, 93
  - for liver disease, 93
  - for oliguric renal failure, 90
  - hypertonic solutions of, for acute renal failure, 530–531, 530t
  - insulin with, for hyperkalemia, 87, 87t
- 5% Dextrose in water (D5W), 84, 85t
- 10% Dextrose in water (D10W), 85t
- Diabetes insipidus, 526, 650–651
  - thiazides for, 521t, 651
- Diabetes mellitus, 636–644
  - classification of, 636
  - complications of, 637
  - diagnosis of, 636–637
  - glucocorticoids and, 315–316, 327, 328, 641
  - hyperadrenocorticism with, 641, 647
  - hyperosmolar nonketotic, 643
  - insulin for, 626t, 637–640
    - complications of, 640–643
  - oral agents for, 643–644
- Diabetic ketoacidosis, 82, 626t, 642–643
  - fluid therapy in, 93, 642
- Dialysis, 541–542
  - peritoneal, 541, 542
    - for peritonitis, 205
- Diaminopyrimidines. See also *Trimethoprim.*
  - mechanism of action of, 260
  - resistance to, 167–168
  - sulfonamides with. See *Sulfonamides, potentiated;* specific combinations.
- Diarrhea, 496–499
  - acidosis due to, 81
  - acute, 505–506
    - fluid therapy for, 92
  - antibiotic-associated, 201
  - bacterial, 202, 506–507
  - chronic, 507
    - fluid therapy for, 92–93
  - due to large intestinal disease, 507–508
  - viral, 506
- Diastases, for digestive disorders, 503
- Diatomaceous earth, intoxication with, 721t
- Diazepam, as anticonvulsant, 444–446
  - as anxiolytic, 466
  - as appetite stimulant, 482
    - in chronic renal failure, 534t, 538
  - as muscle relaxant, 479, 480
  - as preanesthetic medication, 426
  - constant IV infusion rate for, 769t
  - dosage for, 413t, 435t, 459t, 484t, 534t, 543t, 741t
  - drug interactions with, 479
    - phenytoin, 444
  - for acute seizure management, 437, 444, 445–446
  - for chronic seizure control, 439, 444
  - for emergence delirium after methohexital anesthesia, 427
  - for feline urologic syndrome, 548
  - for hypertonic urethra, 543t, 546
  - for inappropriate elimination in cats, 471
  - for invasive procedures in critical illness, 420
  - for noise phobias, 470
  - for social anxiety in cats, 472
  - for tetanus, 217
  - for tricyclic antidepressant poisoning, 464
  - hepatotoxicity of, 46–47, 466, 471, 482
  - parenteral solutions of, interactions with, 20t
  - pharmacokinetics of, 433–434, 444–445
  - structure of, *434*
  - thyroid effects of, 54t
- Diazinon, 663
- Diazoxide, 741t
- Dichlophenamide, 741t
- Dichlorodiphenyltrichloroethane (DDT), phenytoin interaction with, 444
- Dichlorophene, 268t, 269t, 275
  - toluene with, 276
- Dichlorvos, 268t, 269t, 273, 741t
- Dicloxacillin, 152t, 155–156
  - dosage for, 154t, 742t
  - for pyoderma, 194
  - pharmacokinetics of, 157
  - susceptibility test interpretation for, 134t
- Dicumarol, 121–122, 742t
  - mechanism of action of, *117*
  - phenytoin interaction with, 444
- Dicyclomine, as antiemetic, 487
  - dosage for, 484t, 543t, 742t
  - for hypercontractile bladder, 544
- Didanosine, 243
- Dieldrin, phenytoin interaction with, 444
- Diet, commercial, approximate nutrient content of, 537t
  - drug interactions with, 19, 22t
  - in acute renal failure, 532
  - in chronic renal failure, 532–536, 537t
  - in glomerular disease, 541–542
- Diethylcarbamazine, 268t, 273
  - dosage for, 562t, 742t
  - for heartworm disease, 597
  - for heartworm disease prevention, 273, 597
  - oxibendazole with, 276
  - skin lesions due to, 53, 53t
- Diethylstilbestrol, 681
  - dosage for, 543t, 742t
  - for estrus induction, 682t, 683
  - for hypotonic urethra, 543t, 545
  - for urinary incontinence, 687
  - inappropriate use of, 688t, 689
- Diffusion, passive, drug movement by, 5–6
- Diflorasone, 658t
- Difloxacin, 164
  - dosage for, 154t, 742t
  - for osteomyelitis, 180
  - pharmacokinetics of, 165
  - structure-activity relationship of, 162, *163*
- Digitalis glycosides, 574–577, *574*. See also *Digitoxin; Digoxin.*
  - artifacts in therapeutic monitoring of, 72t
  - intoxication with, 571, 576–577, 721t
  - spironolactone interaction with, 523
- Digitoxin, 577. See also *Digitalis glycosides.*
  - clinical efficacy of, 576
  - dosage for, 562t, 742t
  - parenteral solutions of, interactions with, 20t
  - pharmacokinetics of, 575
  - phenytoin interaction with, 444
  - therapeutic monitoring of, 577
- Digoxin, 573, 577. See also *Digitalis glycosides.*
  - clinical efficacy of, 575–576
  - dosage for, 562t, 742t
  - drug interactions with, 575
    - calcium channel blockers, 564, 575
    - diuretics, 522, 524, 575
    - phenothiazines, 461
    - quinidine, 569, 575
    - thiazides, 522
  - for atrial fibrillation, 587
  - for dilated cardiomyopathy, 583
  - for mitral valve insufficiency, 580, 581
  - indications for, 576
  - intoxication with, 576–577
  - mechanism of action of, 574–575, *574*
  - pharmacokinetics of, 575
    - variability of, 68
      - case studies of, 66, 67
  - structure of, *564*
  - therapeutic monitoring of, 577
    - procedure for, 68
    - reference data for, 63t
- Digoxin Fab, 577
- Dihydrostreptomycin, 160, 742t, 764t
- Dihydrotachysterol, *632, 633*
  - dosage for, 626t, 742t, 767t
  - for hypoparathyroidism, 634
- 1,25-Dihydroxycholecalciferol (calcitriol), *633,* 634
  - dosage for, 534t, 626t, 736t, 768t
  - for hyperparathyroidism, in chronic renal failure, 534t, 539–540
  - for hypoparathyroidism, 626t, 634
- Dilated cardiomyopathy, in cats, 583–584
  - in dogs, 581–583
- Diltiazem, as antiarrhythmic, 572, 573
  - as vasodilator, 561–564
  - constant IV infusion rate for, 769t
  - cyclosporine interaction with, 356
  - dosage for, 534t, 562t, 742t
  - for dilated cardiomyopathy, 583
  - for hypertension in chronic renal failure, 534t, 539
  - for hypertrophic cardiomyopathy, 584–585
  - structure of, *564*
- Dimenhydrinate, as antiemetic, *487*
  - dosage for, 608t, 742t
  - for respiratory disease, 608t
- Dimercaprol (BAL), 354t, 742t
  - for gold chelation, 360

Dimethylsulfoxide, 302–303
  as vehicle for topical drugs, 657
  dosage for, 284t, 742t
  for anthracycline extravasation, 336
  for otitis externa, 198
  for renal amyloidosis, 542
  for shock, 590t
  intravesicular, for lower urinary tract disease, 549–550
Diminazene aceturate, 742t
Dinoprost tromethamine, for pregnancy termination, 680, 686
  for pyometra and postpartum metritis, 686
Dioctyl sodium sulfosuccinate, 484t, 661, 742t
Diphacinone rodenticide, half-life of, 121
  vitamin K for poisoning by, 117
Diphemanil methylsulfate, 742t
Diphenhydramine, as antiemetic, 486
  before amphotericin B administration, 226
  dosage for, 484t, 608t, 665t, 742t
  for allergic rhinitis, 608t, 614
  for behavioral modification, 468
  for skin disease, 665t, 666
  parenteral solutions of, interactions with, 20t
  structure of, *487*
  topical, 658t
Diphenoxylate, 416
  dosage for, 484t, 742t
  for diarrhea, 498
Diphenylhydantoin. See *Phenytoin.*
Diphenylmethane cathartics, 501
Diphenylthiocarbazone, 742t
Dips, for antiparasitic drug delivery, 662
Dipyridamole, 123, 743t
Dipyrone, 284t, 743t
Dirofilariasis. See *Heartworm disease.*
Disinfectants, 250–257, 251t. See also *Disinfection;* specific agents.
  characteristics of, by chemical type, 251–254
  defined, 250
  for canine distemper, 245
  for canine parvovirus, 245
  for coronavirus, 247
  for dermatophytosis, 675
  for infectious canine hepatitis, 246
  for parainfluenza virus, 246
  ototoxicity of, 52
  targets for, *251*
Disinfection. See also *Disinfectants;* specific agents.
  defined, 250
  factors affecting, 254–255
  procedures for, 255
Disk diffusion method, for culture and susceptibility testing, 130, *130*
Disodium EDTA, 743t
Disophenol, 743t
Disopyramide, 562t, 570, 743t
Disposition of drugs, 3–13, *4–13.* See also *Pharmacokinetics.*
  determinants of, 6–13
  one-compartment open model of, 4, *5*
  pathologic factors affecting, 19t, 25–29
  pharmacologic factors affecting, 18–25, 19t. See also *Drug interactions.*
  physiologic factors affecting, 19t, 29–37
  species and breed differences in, 35–36
  two-compartment open model of, 4, *5*
Disseminated intravascular coagulation, heparin for, 112t, 121
  in heartworm disease, 594, 595
  in infectious canine hepatitis, 246
  in septic shock, 205, 206
Dissociative anesthesia, 427–428
Distemper, canine, 238t, 245
Distribution, drug, 7–9, *8, 9*
  drug interactions involving, 22–23, 23t
  from topical application, 193
  in pediatric animal, 31t, 32, *32*
  in plasma concentration vs. time curve, 4, *5*
  patterns of, for antimicrobials, 142–143, 142t
  species and breed differences in, 35
  to bone, 179–180
  to bronchial secretions, 182, 182t, *183*
  to central nervous system, 177
  to skin, 193
Distribution half-life, 9
Distribution rate constant, *5,* 9
Distributive shock, 89–90, 588–589. See also *Septic shock.*
Dithiazanine iodide, 743t
  for heartworm disease, 597
Diuresis. See also *Diuretics;* specific drugs.
  fluid-overload, for polyuric renal failure, 90
  for acute renal failure, 529–531, 530t
  for urinary tract infection, 189
  osmotic, for oliguric renal failure, 90
  saline, for hypercalcemia, 94
Diuretics. See also *Diuresis;* specific drugs.
  classification of, 517, *517,* 519t
  drug interactions with, digoxin, 522, 524, 575
    NSAIDs, 522–523, 524–525
  factors limiting response to, 518–520
  for cirrhosis, 525
  for dilated cardiomyopathy, 583
  for heart failure, 525
  for hypercalcemia, 635
  for intracranial hypertension, 452
  for mitral valve insufficiency, 580, 581
  for nephrotic syndrome, 525
  for pulmonary edema, 620
  high ceiling (loop), *517,* 519t, 524–525
    decreased response to, in cirrhosis, 525
    for heart failure, 525
    thiazide interaction with, 522
  indications for, 517
  osmotic, 519t, 520
    for acute renal failure, 529–530
  potassium-sparing, *517,* 519t, 523
  structures of, *518*
  therapeutic use of, 516–518, *516, 517*
  thiazide. See *Thiazide diuretics.*
Divalproex sodium. See *Valproic acid.*
DNA, 384–386, *386*
  bacterial, antimicrobials targeting, 141, *141, 152*
  fluorinated quinolones' effects on, 163, *164*
DNA immunization, 397–398
DNA ligase, 387
Dobermans, dilated cardiomyopathy in, 582
Dobutamine, 578–579
  constant IV infusion rate for, 769t
  dosage for, 562t, 743t
  for dilated cardiomyopathy, in cats, 583–584
    in dogs, 583
  for shock, 206, 579, 590t
  parenteral solutions of, interactions with, 20t
Docohexaenoic acid, for pruritus, 672
Docusate sodium, 500, 743t
Dominance-related aggression, 469. See also *Aggression.*
Domperidone, 484t, 495, 743t
Donors, for blood, 98–99, 99t
    blood collection from, 99–100, *99*
  for bone marrow, 105
Dopamine, 457, *458*
  as inotrope, 578
  constant IV infusion rate for, 769t
Dopamine *(Continued)*
  dosage for, 530t, 562t, 743t
  for acute renal failure, 529, 530t
  for shock, 206, 590t, 591
  in gastric motility, 494, *494*
  in vomiting reflex, 483, *486*
Dopamine agonists, 681. See also specific drugs.
  for estrus induction, 679, 682t, 683–684
  for pregnancy termination, 686–687
Dose. See also *Dosing regimens.*
  adjustment of, in cardiac disease, 28
    in liver disease, 27
    in renal disease, 26
    with pharmacokinetic profile, *68,* 70–71
    without pharmacokinetic profile, 71
  calculation of, 13–14, 710
    based on body surface area, 16, 333–334, 333t
    for accumulating drug, 16
    for anticancer drugs, 333–334, 333t
    for blood administration, 102–104, 102t, *103*
  loading, *14,* 15, 436
    calculation of, 64, *68*
    therapeutic drug monitoring and, 64–66, *65*
  maintenance, *14,* 15–16
Dose-response relationship, 3, *3*
Dosing interval. See also *Dosing regimens.*
  adjustment of, in renal disease, 26
  calculation of, 14–15
  elimination half-life and, 14–15, 434–435
    fluctuation of plasma concentration and, *14,* 15, 435
    in drug accumulation, *14,* 15–16, 15t, 435
Dosing regimens. See also *Dose; Dosing interval.*
  cross-species extrapolation of, 35–36, 37–38
  fixed, 13–16, *14,* 15t
  formulas for calculating, *68*
  recommended, 733t–775t
  trial-and-error modification of, 60–61
Double-burst stimulation, for neuromuscular blockade monitoring, 477, *478*
Doxacurium chloride, 474t, 475–476
Doxapram, 743t
Doxepin, 462, 668
  dosage for, 459t, 665t
  for pruritus, 671
  for psychogenic dermatosis, 471
Doxorubicin, 339–340, 743t
  extravasation of, 335, 340
  hemorrhagic colitis due to, 335
  liposomal delivery system for, 379–380
  parenteral solutions of, interactions with, 20t
Doxycycline, 152t, 169
  bronchial penetration by, 182, 182t
  constant IV infusion rate for, 769t
  dosage for, 154t, 177t, 743t
  for brucellosis, 207
  for ehrlichiosis, 212
  for leptospirosis, 208
  for Rocky Mountain spotted fever, 213
  minimum inhibitory concentrations for selected organisms for, 132t
  parenteral solutions of, interactions with, 20t
  slow-release preparation of, for periodontal disease, 200
  susceptibility test interpretation for, 134t
Doxylamine succinate, 743t
Droperidol, 487, 745t
Drowning, near, 620–621
Drug(s), approval process for, 694–696
    costs of, for animal drugs, 696–697
  defined, 694

Drug(s) *(Continued)*
  generic, 699
  generic and trade names of, 726t–730t
  orphan, 696
  schedule, 411–412, 699, 699t
Drug Enforcement Agency, reporting adverse scheduled drug reactions to, 701
Drug interactions, 18–25
  case studies of, 64, 69
  in therapeutic drug monitoring, 72t
  pharmaceutical, 18–22, 20t–22t
  pharmacodynamic, 24–25, 24t
  pharmacokinetic, 22–24, 22t–24t
Drug monitoring. See *Therapeutic drug monitoring.*
Drug-metabolizing enzymes. See under *Enzymes.*
Dusting powders, 657
Dwarfism, pituitary, 650
Dynorphins, 407, *408*
  in gastrointestinal tract, 497
Dystocia, 682t, 687

E

Ear, cleansing of, for otitis externa, 196–197, 199
  drug-induced disease of. See *Ototoxicity.*
  infection of. See *Otitis* entries.
Ear mites, 199
  ivermectin for, 665t, 669
Echocardiograpy, in dilated cardiomyopathy assessment, 582
Eczematous dermatitis, drug-induced, 53
Edema, cerebral. See *Cerebral edema.*
  pulmonary. See *Pulmonary edema.*
  treatment of, 516–517. See also *Diuresis; Diuretics;* specific drugs.
Edetate. See *EDTA (ethylenediaminetetraacetate).*
Edrophonium, 484t, 743t
  for myasthenia gravis diagnosis, 484t, 503
  for neuromuscular blockade reversal, 479, 479t
EDTA (ethylenediaminetetraacetate), as germicide, *251,* 253
  calcium disodium, 737t, 743t
    parenteral solutions of, interactions with, 20t
  disodium, 743t
  sodium, for hypercalcemia, 626t, 635
  with Tris buffer, 253
    for otitis externa, 198, 198t
Ehrlichiosis, 211–212
Eicosanoids. See also *Prostaglandin(s).*
  in inflammatory response, 282–283, *282,* 283t, *285*
  in septic shock pathogenesis, 304
  pain and, 407
Eicosapentaenoic acid, 666
  for pruritus, 672
  for skin disease, 667–668, 667t
Electrical nerve stimulation, for neuromuscular blockade monitoring, 476–478, *477, 478*
Electrocardiography, in hyperkalemia diagnosis, 531
Electrolytes, 75–94. See also specific electrolytes.
  corticosteroids' effects on, 316
  renal transport of, 515–516, *516, 517*
  therapy with, 85t, 86–87, 87t
Electromechanical dissociation, 593
Electromyography, for evoked response measurement, in neuromuscular blockade monitoring, 478
Electroporation, 391
Elimination, drug, 11–13, *12, 13.* See also *Excretion of drugs.*
    antimicrobial efficacy and, 143
    in plasma concentration vs. time curve, 4, *5*
Elimination half-life, 11–13, *12*
  calculation of, from therapeutic drug monitoring data, *65, 68,* 70–71
  dosing interval and, 14–15, 434–435
    fluctuation of plasma concentration and, *14,* 15, 435
    in drug accumulation, *14,* 15–16, 15t, 435
  therapeutic drug monitoring and, 62–67, *65*
  variability of, case studies of, 66, 67
    over course of treatment, 38
    sample collection for identifying, 68
  volume of distribution and, 8, *8,* 13
Elimination rate constant, *5,* 11
Embolism. See also *Thromboembolism.*
  in infective endocarditis, 203
  pulmonary. See *Pulmonary embolism.*
Emesis. See *Vomiting.*
Emetics, 483–486
Emetine, 743t
Emollients, as vehicles for topical drugs, 657
Emphysema, 617
Empyema, 184, 621
Emulsions, as vehicles for topical drugs, 656–657
Enalapril, 565, 566
  dosage for, 534t, 562t, 743t
  for dilated cardiomyopathy, 583
  for hypertension, 586
    in chronic renal failure, 534t, 539
  for mitral valve insufficiency, 580
  structure of, *564*
Encephalopathy, hepatic. See *Hepatic encephalopathy.*
Endocarditis, infective, 127t, 202–203
Endocrine system, disorders of, 624–651. See also specific disorders.
  drug reactions involving, 53–55, 54t
Endometritis. See also *Metritis.*
  bacterial, 190
Endorphins, 407, 408, *408*
  in gastrointestinal tract, 497
Endothelin, in heart failure, 559
Endothelium-derived relaxing factor. See *Nitric oxide.*
Endotoxic shock. See *Septic shock.*
Endotoxin, in infective endocarditis, 203
  in peritonitis, 204
  in pyometra, 190–191
  in septic shock pathogenesis, 304
  release of, in response to antimicrobial therapy, 145
Endotoxin antisera, 743t
Enemas, 501
  phosphate, 762t
    adverse effects of, 50–51, 501
Energy requirements, in chronic renal failure, 535
Enflurane, 743t
Enilconazole, 228–229, 659t
  aerosol therapy with, 615t
  dosage for, 232t, 743t
  for aspergillosis, 234, 615
  for dermatophytosis, 675
    adverse effects of, 674
  for *Malassezia* infection, 233
Enkephalins, 407, 408, *408*
  in gastrointestinal tract, 497
Enoxaparin, 120
Enrofloxacin, 164
  adverse reactions to, 165, 166
  aerosol therapy with, 615t
Enrofloxacin *(Continued)*
  central nervous system toxicity of, 51t
  dosage for, 154t, 665t, 743t
  for bacterial pneumonia, 183, 619
  for ehrlichiosis, 212
  for leptospirosis, 208
  for otitis externa, 198t, 199
  for pyoderma, 193, 194, 195
  for Rocky Mountain spotted fever, 213
  for urinary tract infections, 187t
  minimum inhibitory concentrations for selected organisms for, 132t
  pharmacokinetics of, 165–166, *166*
  relative efficacy of, *133*
  resistance to, 165
  structure-activity relationship of, 162, 163, *163*
  susceptibility test interpretation for, 135t
  theophylline interaction with, case study of, 69
Entamoeba histolytica infection, 508
Enteritis, bacterial, 506–507
  garbage, 505
  parvovirus, 238t, 244–245, 506
    fluid therapy in, 92, 245
  viral, 506
Enterocolitis, hemorrhagic, due to *Bacillus piliformis,* 506
Enterohepatic circulation, 11, *12*
Enterotoxicosis, 508
Enterotoxins, 201–202
Environmental manipulations, in pain control, 407–408
Environmental Protection Agency, reporting adverse pesticide reactions to, 699
Enzymes. See also specific enzymes and enzyme groups.
  digestive, 503
  drug-metabolizing, 10
    anticonvulsants' effects on, 434
    drug interactions involving, 23–24, 23t, 64
    hormonal effects due to induction of, 53–55
    in pediatric animal, 33
    species and breed differences in, 36
    therapeutic failure due to, case study of, 62
    thyroid disease's effects on, 28
Eosinophilic granuloma complex, feline, 367, 503
    glucocorticoids for, 325, 503
Eosinophilic infiltrates, pulmonary, 619–620
Ephedrine, adrenocortical effects of, 54t
  as bronchodilator, *604,* 607, 608t
  as decongestant, 614
  dosage for, 544t, 608t, 743t
  for hypotonic urethra, 543t, 545
  for shock, 590t
Epidermis, 654
  lipid synthesis in, 655
Epidural analgesia, 413t, 422
Epilepsy. See *Seizures.*
Epinephrine, as bronchodilator, *604,* 607, 608t
  as inotrope, 579
  constant IV infusion rate for, 769t
  dosage for, 562t, 608t, 744t
  for bronchial disease, 617
  in cardiopulmonary resuscitation, 592, 593
  in potassium regulation, 77
  parenteral solutions of, interactions with, 20t
  topical, for hemostasis, 116
Epirubicin, 340–341
Epoetin alfa. See *Erythropoietin, recombinant human.*
Epsiprantel, 268t, 269t, 274, 744t

- Epsom salts. See also *Magnesium sulfate.*
  - as astringent, 657
  - as cathartic, 500
- Equine chorionic gonadotropin, 679, 681
  - for estrus induction in cats, 684
- Ergocalciferol, *633.* See also *Vitamin D.*
  - dosage for, 626t, 744t, 767t
  - for hypoparathyroidism, 626t, 634
  - structure of, *632*
- Ergosterol, 634
  - amphotericin B's affinity for, 224, *225*
  - azole drugs' effects on, 227
- Erythema multiforme, drug-induced, 52
- Erythematous dermatitis, drug-induced, 53
- Erythrocytes. See *Red blood cell(s).*
- Erythromycin, 170
  - antipruritic effect of, 671
  - bronchial penetration by, 182, 182t
  - central nervous system toxicity of, 51t
  - dosage for, 154t, 744t
  - drug interactions with, cyclosporine, 356
    - diazepam, 479
  - efficacy of, pH and, 140
  - for urinary tract infections, 187t
  - gastrointestinal disease due to, 50, 193
  - parenteral solutions of, interactions with, 20t
  - prokinetic effect of, 494, *494,* 505, 508
  - spectrum of activity of, 152t, 170
  - structure of, *159*
  - susceptibility test interpretation for, 135t
- Erythropoietin, 110–113, 377, 744t
  - for feline leukemia virus infection, 248
  - mechanism of action of, *108,* 110–111
  - recombinant human, 110, 111, 391–393, *392,* 392t
    - dosage for, 112t, 534t
    - for anemia of chronic renal failure, 534t, 539
    - hematologic disorders due to, 56, 56t, 111, 392, *392*
    - skin lesions due to, 53, 53t, 111
- Escharotics, 661
- *Escherichia coli,* enteritis due to, 506
  - minimum inhibitory concentrations for selected antimicrobials for, 132t
  - urinary tract infection due to, 187
- Esmolol, 562t, 572, 744t
  - constant IV infusion rate for, 769t
- Esophageal disease, 503–504. See also *Gastroesophageal reflux.*
  - infectious, 200
- Estradiol cypionate, 744t. See also *Estrogens.*
  - inappropriate use of, 688t, 689
- Estrogens, 679
  - adrenocortical effects of, 54t
  - commercial availability of, 681
  - for estrus induction, 682t, 683
  - for hypotonic urethra, 545
  - hematologic disorders due to, 56, 56t
  - in gonadotropin regulation, 678
  - inappropriate use of, 688t, 689
  - thyroid effects of, 54t
  - toxicity of, in dog, 679
- Estrus, induction of, 681–684, 682t, *683*
  - prevention of, 682t, 685–686
  - split, 684
- Ethacrynic acid, 519t, 524
  - dosage for, 521t, 744t
- Ethambutol, 154t, 210, 744t
- Ethanol, adrenocortical effects of, 54t
  - antidiuretic hormone secretion and, 526
  - as germicide, 251
  - dosage for, 744t, 769t
- Ethical considerations in clinical trials, 702–704
- Ethosuximide, 744t
- Ethoxzolamide, 744t
- Ethyl lactate, 658t
- Ethylene glycol intoxication, 721t, 722t
  - acidosis due to, 82
  - hemodialysis for, 542
  - hypocalcemia due to, 531
  - sodium bicarbonate therapy for, 88
- Ethylene oxide sterilization, 253
- Ethylenediamine dihydroiodide, as expectorant, 613
- Ethylenediaminetetraacetate (EDTA). See *EDTA (ethylenediaminetetraacetate).*
- Ethylisobutrazine, 744t
- Etidronate, 635, 744t
- Etodolac, 292
  - adverse effects of, 287t, 292
  - dosage for, 284t, 744t
  - selectivity of, for cyclooxygenase isoforms, 284
- Etomidate, 744t
  - adrenocortical effects of, 54t
  - for acute seizure management, 438
  - for anesthesia induction, 428
  - for head trauma, 453
- Etretinate, 660, 661, 744t
- Euphoria, due to glucocorticoids, 319
- Euthanasia solution, 744t
- Evening primrose oil, for pruritus, 672
- Excretion of drugs, biliary, 10–11, *12*
    - pathologic factors affecting, 27
  - drug interactions involving, 24, 24t
  - renal, 10, *11*
    - pathologic factors affecting, 25–26, 25t
    - urinary tract infection therapy and, 187–188
- Exfoliation, generalized, drug-induced, 53
- Exons, 386, *386*
- Expectorants, 613–614
- Extracellular fluid, 75
  - drug distribution to, 9
  - in geriatric animal, 30
  - in pediatric animal, 31t, 32, *32*
  - osmolality of, 75
  - pH of, determinants of, 77–78
  - reduction of. See also *Diuresis; Diuretics;* specific drugs.
    - strategies for, 516–517
  - renal regulation of, 515, 516
- Extralabel drug use, 696–698, *697,* 698t
- Extrapyramidal effects, of metoclopramide, 495
- Extravasation of cytotoxic drugs, 335–336
- Extravascular administration. See also specific route.
  - plasma concentration vs. time curve for, 4, *5*
- Eye disease, due to hypertension, 585-586
  - glucocorticoids for, 326
  - herpetic, 247, 396
  - organisms causing, 128t

F

- Famciclovir, 241
- Famotidine, 484t, 744t
  - for gastrointestinal ulceration, *489,* 490
    - due to NSAIDs, 504
  - structure of, *487*
- Fatty acids, 666, *667*
  - adverse effects of, 668
  - essential, 713t
    - dosage for, 744t
  - for canine seborrhea, 673
  - for pruritus, 672
  - omega, 742t
    - for inflammatory bowel disease, 509
  - omega-3, for chronic renal failure, 535
- Fatty acids *(Continued)*
    - for glomerular disease, 541–542
    - for skin disease, 666–668, 667t
  - omega-6, for skin disease, 666–668, 667t
- Fear behavior, 470
- Febantel, 268t, 269t, 271, 744t
  - in combination anthelmintics, 276
- Fecal softeners, 500
- Felbamate, 435t, 448–449, 744t
- Feline eosinophilic granuloma complex, 367, 503
  - glucocorticoids for, 325, 503
- Feline hematuria, idiopathic, 547–548
- Feline immunodeficiency virus, 238t, 248–249
- Feline infectious peritonitis, 238t, 246–247
  - interferon α for, 247, 373–374
  - pericardial effusion in, 588
- Feline leukemia virus infection, 238t, 247–248
  - interferon α for, 248, 374–375, 395–396
  - zidovudine for, 243, 248
- Feline oncornavirus-associated cell membrane antigen (FOCMA) antibodies, 362
- Feline panleukopenia, 238t, 246
- Feline urologic syndrome, 547–548
- Feline viral respiratory disease, 238t, 247
- Femoral artery, blood collection from, 100
- Fenbendazole, 268t, 269t, 271
  - dosage for, 745t
  - for giardiasis, 265, 507
  - for parasitic lung disease, 619
  - for protozoal infections, 258t
  - for salmon poisoning, 506
- Fenoxycarb, 663
- Fentanyl, 414–415
  - constant IV infusion rate for, 769t
  - dosage for, 413t, 426t, 745t
  - epidural administration of, 422
  - in pediatric animal, 34
  - pharmacokinetics of, 410, 414–415
  - receptor selectivity of, 409t
  - structure of, *409*
  - transdermal formulation of, 413t, 414–415, *414,* 747t
- Fenthion, 663, 668, 669–670, 745t
- Ferric cyanoferrate, 745t
- Ferric sulfate, topical, for hemostasis, 116
- Ferritin, in iron absorption, *109,* 110
- Ferrous sulfate, 745t
  - with erythropoietin, for anemia of chronic renal failure, 540
- Fertilizer ingestion, 721t
- Fetus. See also *Pregnancy.*
  - atropine's effects on, 425
  - drug disposition in, 34–35
  - fluorinated quinolones' safety for, 190
  - opioids' effects on, 410, 411
  - phenytoin's effects on, 443
- Fibrinogen, topical, 116
- Fibrinolysin inhibitors, for hemostasis, 118
- Fibrinolytic agents, 122–123
- Fibrinopeptides, in inflammatory response, 283t
- Fibroblasts, in inflammatory response, 282
- Fibronectin, as immunostimulant, 362
  - dosage for, 354t
- Fibrous tissue, at infection site, antimicrobial efficacy and, 139, *140*
- *Filaroides hirthi* infection, 619
- Filgrastim, 746t. See also *Granulocyte colony-stimulating factor.*
- Filters, for blood administration, 102, *102*
- Finasteride, 680, 681, 745t
  - for benign prostatic hyperplasia, 688
- Fipronil, 663
- First-order elimination, 12–13, *12*
- First-pass metabolism, bioavailability and, 6–7, *7*

First-pass metabolism *(Continued)*
    in liver disease, 27
  dosing regimen extrapolation and, 37
Fish oil, for inflammatory bowel disease, 509
  for pruritus, 672
  for skin diseases, 666–668, 667t
Fixed dosing regimens, 13–16, *14*, 15t
Fixed drug eruptions, 52, 53
Flavoxate, 745t
Flea collars, 662
  skin lesions due to, 53, 53t
Flea insect growth regulators, 663
Flora, normal. See *Normal flora.*
Florfenicol, 154t, 745t
Flow-limited drugs, 10, 26
  hepatic disease's effects on, 26–27, 27t
  in geriatric animal, 29
Fluconazole, 228, 229
  dosage for, 232t, 745t
  for blastomycosis, 233
  for coccidioidomycosis, 234
  for cryptococcosis, 234
  for histoplasmosis, 233
  mechanism of action of, 227
  spectrum of activity of, 223t, 227, 228
  structure of, *224*
5-Flucytosine, 229–230
  dosage for, 232t, 745t
  for candidiasis, 233
  skin lesions due to, 53, 53t
  spectrum of activity of, 223t, 230
  structure of, *224*
Fludrocortisone, *320*, 322
  dosage for, 626t, 745t
  for hypoadrenocorticism, 626t, 649
  with mitotane therapy for hyperadrenocorticism, 647
Fluid compartments, 75. See also *Extracellular fluid.*
  in geriatric animal, 30, *30*
  in pediatric animal, 31t, 32, *32*
Fluid homeostasis, 75–76
  corticosteroids' effects on, 316
  renal regulation of, 515–516, *516*, *517*
Fluid therapy, 82–85, 83t–85t
  additives in, 84, 84t
  deficit determination in, 83, 83t
  determining adequacy of, 85
  electrolyte composition of commercial products for, 85t
  fluid choice for, 83–84, 84t, 85t
  for acute renal failure, 90–91, 529, 531
  for canine parvoviral enteritis, 92, 245
  for cardiac disease, 91–92
  for cardiopulmonary resuscitation, 592
  for diabetic ketoacidosis, 93, 642
  for gastrointestinal disorders, 92–93, 202, 504
  for head trauma, 452
  for heat stroke, 91
  for hepatic disease, 93
  for hypercalcemia, 94, 635
  for hypoadrenocorticism, 648
  for hypocalcemia, 93–94
  for hypoglycemia, 93
  for pancreatic disease, 93, 511
  for renal disease, 90–91
  for shock, 88–90, 206, 590t, 591
  in pediatric animal, 33
  in surgical patient, 94
  intensive, aminoglycosides with, 70
  maintenance requirements in, 83, 531
  route of administration for, 84–85
Flumazenil, 484t, 509, 745t
Flumethasone, 317t, 745t
Flunixin meglumine, 293

Flunixin meglumine *(Continued)*
  adverse effects of, 287t, 293
  dosage for, 284t, 745t
  for gastric dilatation/volvulus, 505
  for sepsis syndrome, 207
  for shock, 590t, 591
    in parvovirus enteritis, 506
  parenteral solutions of, interactions with, 20t
  selectivity of, for cyclooxygenase isoforms, 284
Fluocinolone, 54t, 658t
Fluocinonide, 658t
Fluoracetate, intoxication with, 721t
Fluoride, intoxication with, 721t
Fluorocarbons, as blood substitutes, 105
5-Fluorocytosine. See *5-Flucytosine.*
5-Fluorouracil, 54t, 343, 745t
Fluoxetine, 465
  dosage for, 459t, 665t, 745t
  for acral lick dermatitis, 469, 673
  for dominance-related aggression, 469
  for inappropriate elimination in cats, 471
  for interdog aggression, 469
  for psychogenic alopecia, 672
  for self-mutilation, 465, 469
  for separation anxiety, 470
  for skin diseases, 665t, 668
  structure of, *460*
Fluoxymesterone, 112t, 745t
Flurazepam, 745t
Flurbiprofen, 745t
FOCMA (feline oncornavirus-associated cell membrane antigen) antibodies, 362
Folic acid, 108–109, 714t
  deficiency of, due to triamterene, 523
  dosage for, 112t, 745t
  phenytoin interaction with, 444
  synthesis of, antimicrobials targeting, *152*
    sulfonamides' effects on, 167, *167*
Folinic acid (leucovorin), 109
  dosage for, 112t, 745t, 750t
  with methotrexate, 342
Follicle-stimulating hormone, 678–679, *679*
  commercial availability of, 681
  dosage for, 745t
  for estrus induction, 683
  for hypogonadism, 688
Food and Drug Administration. See also *Regulation of drugs.*
  adverse drug reaction reporting to, 57–58, 699–701
  compassionate use rules of, 696, 698
  compounding guidelines of, 698
  drug approval process of, 694–696
    costs of, for animal drugs, 696–697
  drug definition of, 694
  drug regulation by, 693–701
  extralabel drug use guidelines of, 696–698, *697*, 698t
  generic drug regulations of, 699
  regulatory discretion rules of, 698
  requesting pharmacologic study data from, 37
Formaldehyde, *251*, 252
  intoxication with, 722t
Formalin, as disinfectant, for dermatophytosis, 675
Foscarnet, 242, 746t
Fractional kill hypothesis, 331, 331t
Free radicals. See *Lipid peroxidation; Oxygen radicals.*
Freedom of information request, for pharmacologic study data, 37
Freezing, parenteral solution shelf life and, 18–19
Fructose, hepatoprotective effect of, 502

Fungal infections, 222–234. See also specific infections.
  intestinal, 507
  of middle ear, 178
  of nose, 615
  predisposing factors for, 222
  pulmonary, 619
  subcutaneous, 234
  systemic, 233–234
  yeast-like, 232–233
Fungi, characteristics of, 232
Furazolidone, 172, 746t
  for coccidiosis, 261
  for giardiasis, 265, 507
  for protozoal infections, 258t
Furosemide, 519t, 521t, 524–525
  constant IV infusion rate for, 769t
  dosage for, 521t, 530t, 534t, 746t
  for acute renal failure, 529, 530t
  for ascites, 511
  for dilated cardiomyopathy, 583
  for hypercalcemia, 94, 521t, 524, 635
  for hypertension, in chronic renal failure, 534t, 539
    in glomerular disease, 542
  for intracranial hypertension, 452
    in hepatic encephalopathy, 509
  for nephrotic syndrome, 91
  for ruptured chordae tendineae, 581
  for shock, 590t
  metabolic alkalosis due to, 82
  ototoxicity of, 52, 524
  parenteral solutions of, interactions with, 20t
  structure of, *518*
  thyroid effects of, 54t

G

GABA (γ-aminobutyric acid), 457–458
Gabapentin, 449, 746t
Gamma-aminobutyric acid (GABA), 457–458
Gammaglobulin, human, 362
    dosing regimen for, 354t, 746t, 747t
    for immune-mediated hemolytic anemia, 365
Gamma-linolenic acid (GLA), 666
  for pruritus, 672
  for skin disease, 667, 667t, 668
Ganciclovir, 241–242
Garbage ingestion, 722t
  enteritis due to, 505
Gastric acid secretion, drugs modifying, 489–491, *489*
  opioids' effects on, 498
  physiology of, 489, *489*
  rebound, after histamine$_2$-receptor antagonist therapy, 490
Gastric dilatation/volvulus, 505
  shock due to, 89
Gastrin, in gastric acid secretion, 489, *489*
Gastrinoma, 491
Gastritis, acute, 200–201, 504
  histamine$_2$-receptor antagonists for, 490
Gastroenteritis, hemorrhagic, 507
Gastroesophageal reflux, esophagitis due to, 504
  histamine$_2$-receptor antagonists for, 491
Gastrointestinal tract, bacterial infections of, 200–202, 506–507, 508
    organisms causing, 127t
  disease of. See also specific diseases.
    drug-induced, 49–50, 50t
    due to cancer chemotherapy, 50, 335
    due to cisplatin, 344
    due to glucocorticoids, 319, 326–327
    due to NSAIDs, 50, 287–288, *288*, *289*, 504–505

- Gastrointestinal tract *(Continued)*
    - due to selective serotonin reuptake inhibitors, 465
    - due to uremia, 538
    - fluid therapy for, 92–93
    - treatment of, 503–512
  - drugs acting on, 482–512, 484t–485t. See also specific drugs and classes of drugs.
    - structures of, *487*
  - function of, agents promoting, 503
  - glucocorticoids' effects on, 319
  - hemorrhage in, in chronic liver disease, 510
  - motility of, 493–494, 496, *497*
    - drug interactions due to changes in, 21, 22, 22t
    - drugs affecting, 494–498, *497*
    - infection and, 201
    - opioids' effects on, 497–498
    - treatment of disorders of, 505
  - mucosal barrier of, damage to, in shock, 589–590
  - normal flora of, 127t, 201
    - prophylactic suppression of, 218
  - of geriatric animal, 29
  - opioids' effects on, 412
  - secretion in, 496
    - drugs acting on, 496–501
  - ulceration of, 504
    - due to NSAIDs, 50, 287–288, *288, 289,* 504–505
    - glucocorticoid therapy and, 319, 326–327, 328, 504
    - histamine$_2$-receptor antagonists for, *489,* 490–491
    - in acute liver failure, 509
    - in chronic liver disease, 510
    - pathophysiology of, 488–489
    - spironolactone and, 523
- G-CSF. See *Granulocyte colony-stimulating factor.*
- Gel(s), as vehicles for topical drugs, 657
- Gelfoam, 116, *116*
- Gemfibrozil, 746t
- Gene gun delivery, for DNA immunization, 397
- Gene therapy, future directions in, 398–399
- Generic drugs, 699
- Generic names, trade names and, 726t–730t
- Genetic engineering. See *Recombinant technology.*
- Genital tract, bacterial infections of, 128t, 190–191
  - normal flora of, 128t
- Gentamicin, 159
  - adverse reactions to, *42*
  - aerosol therapy with, 615t
  - dosage for, 155t, 177t, 746t
  - dose adjustment for, in pediatric animal, 33
    - in renal disease, 26
  - for otitis externa, 197t
  - for surgical prophylaxis, 219
  - for urinary tract infections, 187t
  - intensive fluid therapy with, case study of, 70
  - minimum inhibitory concentrations for selected organisms for, 132t
  - nephrotoxicity of, *42,* 161
    - furosemide and, 529
  - parenteral solutions of, interactions with, 20t
  - relative efficacy of, *133*
  - structure of, *159*
  - susceptibility test interpretation for, 135t
  - therapeutic monitoring data for, 63t
- Gentian violet, 233
- Geriatric animals, defined, 29
  - drug disposition changes in, 29–30, *30*
- Geriatric animals *(Continued)*
  - opioid pharmacokinetics in, 410
  - pain control in, 419
- Germicides, 250–257, 251t
  - characteristics of, by chemical type, 251–254
  - defined, 250
  - selection of, 254–255
  - targets for, *251*
  - use of, 255–257
- Giardiasis, 258t, 264–265, *264,* 485t, 507
- Gingivitis, clindamycin for, 170
  - glucocorticoids for, 325
- GLA (γ-linolenic acid), 666
  - for pruritus, 672
  - for skin disease, 667, 667t, 668
- Glass, drug binding to, 19
- Glauber's salt, 500
- Glaucoma, 521t, 522
- Glibenclamide, 626t, 644
- Glipizide, 626t, 643–644, 746t
- Glomerular disease, 540–541
- Glomerular filtration, in drug excretion, 10, *11*
  - pathologic factors affecting, 25
- Glomerular filtration rate, species differences in, 36
- Glomerulonephritis, 540–541
- Glomerulotubular balance, 76
- Glucagon, dosage for, 746t
  - in glucose regulation, 636
- Glucocorticoid(s), 313–328. See also specific agents.
  - adverse effects of, 326–327
    - in renal failure, 538
  - alternate-day therapy with, 323, 326, 664
  - antidiuretic hormone secretion and, 526
  - anti-inflammatory effects of, 316t, 317, *317*
  - as anticancer drugs, 346–347
  - as antiemetics, 488
  - before amphotericin B administration, 226
  - carbohydrate metabolism and, 315–316, 327, 328, 641
  - central nervous system toxicity of, 51t, 326
  - contraindications to, 327–328
  - endogenous, regulation of, 313–314, *314*
  - for acute pancreatitis, 511
  - for asthma, 617–618
  - for bacterial meningitis, 177–178
  - for canine distemper, 245
  - for chronic liver disease, 510
  - for diarrhea, 498
  - for feline chronic progressive polyarthritis, 368
  - for feline eosinophilic granuloma complex, 325, 503
  - for feline urologic syndrome, 547
  - for gastroesophageal reflux, 504
  - for glomerular disease, 541
  - for head trauma, 452
  - for heartworm disease, 594, 595, 596
    - in cats, 598
  - for hypercalcemia, 635
  - for hypoadrenocorticism, 648–649
  - for inflammatory bowel disease, 508
  - for otitis externa, 197t, 198, 198t, 199, 323
  - for otitis media, 178
  - for pemphigus, 366
  - for pericardial effusion, 588
  - for pruritus, 670, 671
    - in combination therapy, 672
  - for respiratory disease, 323–324, 608t, 619
  - for rheumatoid arthritis, 368
  - for sepsis syndrome, 206–207, 325
  - for shock, 89, 306, 325, 590t, 591
    - in parvovirus enteritis, 506
  - for skin diseases, 664–665, 665t
- Glucocorticoid(s) *(Continued)*
  - for thoracolumbar disc extrusion, 453–454
  - gastrointestinal ulceration and, 319, 326–327, 328, 504
  - hepatotoxicity of, 45, 327
  - immunosuppressive actions of, 306, 316t, 317–318, *318,* 327
  - indications for, 323–326
  - interference with hypothalamic-adrenal axis by, 55, 323, 326, 327
  - interference with thyroid function by, 54t, 55, 327, 629
  - mechanism of action of, 314–315, 314t, *315*
  - mineralocorticoid activity of, 316
    - hypoadrenocorticism treatment and, 326
    - structure and, 319, *320*
  - monitoring during therapy with, 664–665
  - pharmacokinetics of, 319–320
  - physiologic effects of, 315–319, 316t, *317, 318*
  - preparations of, 317t, 321–322
    - "depo," 321
  - receptors for, 314–315, 314t, *315*
  - resistance to, 315
  - seizures due to, 328, 439
  - skin lesions due to, 53, 53t
  - structure-activity relationship of, 320, *320*
  - therapeutic use of, 322–326
  - thiazide interaction with, 523
  - topical, 321, 658t, 661
    - for pruritus, 670
  - withdrawal of, 323, 326
- Glucocorticoid responsive elements, 314
- Glucosamines, for osteoarthritis, 300
  - for septic arthritis, 181
  - for urinary tract infection, 189
- Glucose. See also *Dextrose* entries.
  - hepatoprotective effect of, 502–503
  - in commercial fluids, 85t
  - in extracellular fluid osmolality, 76
  - metabolism of, 636
    - glucocorticoids and, 315–316, 327, 641
    - impaired, due to triamterene, 523
- Glucose tolerance tests, 626t, 637
- Glucose-40, 746t
- α-Glucosidase inhibitors, for diabetes mellitus, 644
- Glucuronidation, in drug metabolism, 10, *10*
  - species differences in, 36
- Glutamate, 458
  - in brain injury, 450
- Glutaraldehyde, as germicide, 252
- Glutathione conjugation, feline susceptibility to methemoglobinemia and, 37
  - in drug metabolism, 10, *10*
- Glutathione peroxidase, selenium and, 502
- Glyburide, 746t
- Glycerin, as ceruminolytic, 661
  - as diuretic, 521t
  - as vehicle for topical drugs, 657
  - dosage for, 521t, 746t
- Glyceryl guaiacolate, 746t
- Glyceryl monoacetate, 746t
- Glycohemoglobin measurement, in insulin therapy monitoring, 640
- Glycoproteins, in tracheobronchial secretions, 604
- Glycopyrrolate, as antiemetic, *487,* 488
  - as bronchodilator, *604,* 608t, 610
  - as preanesthetic medication, 425
  - dosage for, 484t, 608t, 746t
  - for tetanus, 217
  - parenteral solutions of, interactions with, 20t
- Glycosaminoglycans, 118
  - in articular cartilage, 296, *298*
  - polysulfated, dosages for, 284t, 758t

- Glycosaminoglycans *(Continued)*
    - for osteoarthritis, 297–299
    - for septic arthritis, 181
    - for urinary tract infection, 189
- GM-CSF. See *Granulocyte-macrophage colony-stimulating factor.*
- Gold compounds, 354t, 359–360, 746t
  - for pemphigus, 366
  - skin lesions due to, 53, 53t, 360
- Gonadal steroid(s), 679–680. See also specific agents.
  - commercial availability of, 681
- Gonadal steroid inhibitors, 680. See also specific agents.
  - commercial availability of, 681
- Gonadorelin, 681
- Gonadotropin(s), 678–679, *678, 679*
  - chorionic, 738t, 746t. See also *Equine chorionic gonadotropin; Human chorionic gonadotropin.*
  - commercial availability of, 681
  - for estrus induction, 682t, 683
  - inappropriate use of, 688–689, 688t
- Gonadotropin-releasing hormone, 677
  - commercial availability of, 681
  - dosage for, 746t
  - for cryptorchidism, 687
  - for estrus induction, 681, 682t
  - for follicular ovarian cyst, 685
  - for ovulatory failure, 684
  - for vaginal hyperplasia/prolapse, 685
- Gonadotropin-releasing hormone analogues, 677, 681
  - for benign prostatic hyperplasia, 687–688
  - for estrus induction, 681–683, 682t
  - inappropriate use of, 688–689, 688t
- Gradient of intestine, 497
- Gram staining, 129, *129*
- Granisetron, 746t
- Granulocyte(s). See *Neutrophils.*
- Granulocyte colony-stimulating factor, 113, 377–378
  - dosage for, 739t, 746t
  - recombinant, canine, 335, 393, *393*
    - for chemotherapy-related myelosuppression, 335, 377
    - human, 335, 392t, 393
- Granulocyte-macrophage colony-stimulating factor, 113, 378
  - in immune response, 350t
  - recombinant, canine, 392t, 393–394
    - human, 392t, 393
- Granulocytopenia. See *Myelosuppression; Neutropenia.*
- Granuloma, lick, 469, 673
- Granulomatosis, pulmonary, 619–620
- Granulopoiesis, growth factors influencing, 113
- Granulopoietin, recombinant human, hematologic disorders due to, 56
- Greyhounds, as blood donors, 98
- Griseofulvin, 223t, 230–231
  - central nervous system toxicity of, 51t
  - dosage for, 232t, 665t, 746t
  - for dermatophytosis, 231, 665t, 674
  - hematologic disorders due to, 56t
  - skin lesions due to, 53, 53t
  - structure of, *224*
- Growth hormone, disorders of, 649–650
  - insulin resistance due to, 641, 649, 650
  - normal concentrations of, 625t
  - recombinant, bovine, 384, 392t, 394–395
    - canine, 395
    - human, 392t, 394–395
  - therapy with, 626t, 650, 746t
  - thyroid effects of, 54t
- Growth retardation, due to glucocorticoids, 327
- Guaifenesin, as expectorant, 614
  - as muscle relaxant, 479–480
  - dosage for, 746t

H

- Hallucinogens, intoxication with, 722t
- Haloperidol, as antiemetic, 487
  - dosage for, 459t
  - for psychogenic alopecia, 672
- Halothane, 429, 746t
  - hepatotoxicity of, 45
  - thyroid effects of, 54t
- Hamamelis, 658t
- Hand hygiene, 256
- Head injury. See *Central nervous system, trauma to.*
- Heart. See *Cardiac* entries.
- Heart failure, approaches to treatment of, 560
  - diuretics for, 525
  - due to doxorubicin, 340
  - fluid therapy in, 91–92
  - pathophysiology of, 558–560, *559*, 565
  - right-sided, with mitral valve insufficiency, 581
  - spironolactone for, 521t
  - thiazides for, 523
- Heart rate, regulation of, 567
- Heartworm disease, 593–598
  - aspirin in, 112t, 123, 595, 596, 611
  - heparin in, 112t, 121, 594–595, 596
    - in cats, 598
  - in cats, 598
    - prevention of, 269t
  - occult, 594
  - pathophysiology of, 593–594
  - prevention of, 597–598
    - diethylcarbamazine for, 273, 597
    - in cats, 269t
    - in dogs, 268t
    - ivermectin for, 268–269, 562t, 597–598
    - ivermectin-pyrantel for, 276–277
    - milbemycin for, 269, 563t, 598
    - moxidectin for, 269–270, 563t, 597, 598
    - selamectin for, 270, 597, 598
  - screening for, in animals on preventative program, 597
  - treatment of, 274–275, 594–597
    - assessment before, 594
- Heat shock protein, 314, *315*
- Heat stroke, 91
- Heavy metal intoxication, 719t
- *Helicobacter* species, gastrointestinal disease and, 201, 505
  - gastrointestinal ulceration and, 489, 505
  - inflammatory bowel disease and, 509
- Helminth infections, 267–277. See also *Heartworm disease;* specific drugs.
  - arsenicals for, 274–275
  - benzimidazoles for, 270–272
  - combination therapy for, 275–277
  - in cats, 269t
  - in dogs, 268t
  - isoquinolones for, 273–274
  - macrolides for, 267–270
  - organophosphates for, 273
  - piperazines for, 272–273
  - prevalence of, 267
  - pulmonary, 619
  - pyrantel for, 272
- Hematinic agents, 107–116. See also specific agents.
  - "shotgun" preparations of, 110
- Hematocrit, in fluid deficit estimation, 83
- Hematopoiesis, 107
  - cyclic, granulocyte colony-stimulating factor for, 377
- Hematopoiesis *(Continued)*
  - drug-induced disorders of, 55–56, *56*, 56t. See also *Myelosuppression.*
- Hematopoietic growth factors, 376–378. See also specific agents.
  - recombinant, 391–394, *392*, 392t, *393*
- Hematuria, idiopathic feline, 547–549
- Hemobartonellosis, 213
- Hemodialysis, 541–542
- Hemoglobin, as acid buffer, 77
  - feline, susceptibility of, to oxidation, 36–37
  - for blood replacement, 749t
  - free, solutions of, as blood substitute, 105
  - iron in synthesis of, 109–110, *109*
- Hemolysis, due to dimethylsulfoxide, 303
  - due to transfusion, 104
- Hemolytic anemia, anabolic steroids for, 115
  - due to hypophosphatemia, 87
  - immune-mediated, 365
    - glucocorticoids for, 326
- Hemorrhage. See also *Hemostasis.*
  - due to heparin therapy, 120
  - due to vitamin K antagonists, 122
  - during surgery, correction for, 94
  - gastrointestinal, in chronic liver disease, 510
  - shock due to, 89, 590t, 591
    - glucocorticoids for, 325, 326
- Hemorrhagic colitis, due to doxorubicin, 335
- Hemorrhagic cystitis, due to cyclophosphamide, 337
- Hemorrhagic enterocolitis, due to *Bacillus piliformis,* 506
- Hemorrhagic gastroenteritis, 507
- Hemosiderin, iron storage as, *109,* 110
- Hemostasis, disorders of. See also specific disorders.
    - in acute liver failure, 509
    - in glomerular disease, 541
  - drugs for, 116–118, *116, 117*
  - drugs limiting, 118–123
  - interleukin-6's effects on, 376
  - pathways of, *115*
  - phenytoin's effects on, 444
  - polysulfated glycosaminoglycans' effects on, 298–299
- Henderson-Hasselbalch equation, 77
- Heparan sulfate proteoglycan, 118
- Heparin, 118–121, *118, 119*
  - constant IV infusion rate for, 769t
  - dosage for, 112t, 120–121, 747t
  - drug inactivation by, 19, 120
  - for collected blood, 100
  - for heartworm disease, 112t, 121, 594–595, 596
    - in cats, 598
  - hematologic disorders due to, 56, 56t, 120
  - in septic shock management, 205, 206
  - interactions involving, 20t, 120
  - low-molecular-weight, 118, 120
  - nonanticoagulant use of, 121
  - overdose of, 722t
    - protamine for, 117
  - structure of, *301*
  - thyroid effects of, 54t, 120
  - transition to warfarin therapy from, 122
- Heparin cofactor II, 118, 119
- Hepatic blood flow, changes in, in cardiac disease, 28
    - in liver disease, 26–27, 27t
  - limitation of drug metabolism by, 10, 26
- Hepatic disease. See *Liver disease;* specific diseases.
- Hepatic encephalopathy, 509
  - due to asparaginase, 346
  - due to carbonic anhydrase inhibitors, 522
  - due to furosemide, 524

Hepatic encephalopathy *(Continued)*
  lactulose for, 500
  prevention of, in fluid therapy for liver disease, 93
Hepatic fibrosis, drug-induced, 45
Hepatic metabolism, bioavailability and, 6–7, *7*
  drug factors affecting, 10
  drug interactions involving, 23–24, 23t
  in geriatric animal, 29–30
  in pediatric animal, 32–33
  pathologic factors affecting, 26–27, 27t
  phases of, 10, *10*
  species and breed differences in, 35–36
Hepatitis, chronic, 509–510
  drug-induced, 45
  infectious canine, 238t, 245–246
Hepatocellular carcinoma, due to anabolic steroids, 114
Hepatotoxicity, 44–47, 44t
  of acetaminophen, 36, *46*, 47, 295
    ascorbic acid for, 295, 484t
  of anabolic steroids, 114
  of anticonvulsants, 45–47, *46*, 434, 439
  of benzodiazepines, 466
  of carprofen, 291
  of diazepam, 46–47, 466, 471, 482
  of dimethylsulfoxide, 303
  of glucocorticoids, 45, 327
  of melarsomine, 595
  of phenobarbital, 45–46, *46*, 441
  of phenytoin, 45, 444
  of primidone, 45, 442
  of thiacetarsamide, 47, 596
  treatment of, 510
Herding breeds, ivermectin toxicity in, 50, 597, 598, 669
Herpes infection, ocular, 247, 396
Herpesviruses, drugs active against, 240–242
Hetacillin, 155t, 157, 747t
  skin lesions due to, 53, 53t
Hetastarch (hydroxyethyl starch), 84, 747t
  constant IV infusion rate for, 769t
  for shock, 89, 590t
  for volume expansion in nephrotic syndrome, 91
Hexachlorophene, *251*, 254
  central nervous system toxicity of, 51t
Hexetidine, for surgical antisepsis, 256
Hippuric acid, for feline urologic syndrome, 547
Histamine, in control of airway caliber, 602, *603*
  in gastric acid secretion, 489, *489*
  in inflammatory response, *282*, 283t
  in respiratory tract inflammation, *604*, 605–606, 605t
  in vomiting reflex, 483, *486*
  release of, due to opioids, 411, 412
  structure of, *487*
Histamine$_1$-receptor antagonists. See *Antihistamines;* specific drugs.
Histamine$_2$-receptor antagonists. See also specific drugs.
  asthma and, 605, 606
  for gastrointestinal ulceration, *489*, 490–491
  in short bowel syndrome management, 507
  with enzyme therapy for exocrine pancreatic insufficiency, 511
Histoplasmosis, 223t, 233
  intestinal, 507
  pulmonary, 619
Hookworms, drugs for, in cats, 269t
    in dogs, 268t
Hormonal therapy. See also specific hormones.
  dosing regimens for, 626t
  for immunomodulation, 359, 363
Hormonal therapy *(Continued)*
  reproductive. See *Reproductive hormones;* specific agents.
  skin lesions due to, 53
  with recombinant products, 392t, 394–395
Hospital Review Committee, 702
Human chorionic gonadotropin, 679
  commercial availability of, 681
  for cryptorchidism, 687
  for estrus induction, 684
  for follicular ovarian cyst, 685
  for hypogonadism, 688
  for ovulatory failure, 684
  for vaginal hyperplasia/prolapse, 685
Humectant, 658t
Hyaluronic acid, dosage for, 284t, 747t
  for osteoarthritis, 299
  for septic arthritis, 181
Hyaluronidase, for vinca alkaloid extravasation, 335
Hybridization, nucleic acid, 387, *389*
Hydralazine, 561
  dosage for, 562t, 747t
  for dilated cardiomyopathy, 584
  for hypertension, 586
    in chronic renal failure, 534t, 539
  for mitral valve insufficiency, 580, 581
Hydrazine sulfate, as appetite stimulant, 482
Hydrocarbon bases, as vehicles for topical drugs, 656
Hydrochlorothiazide, 519t, 522
  dosage for, 521t, 747t
  spironolactone with, 521t, 768t
Hydrocholeretics, 501
Hydrocodone, 416
  as antitussive, 608t, 611–612
  dosage for, 459t, 608t, 665t, 747t
  for behavioral modification, 468
  for skin diseases, 665t, 668
  pharmacokinetics of, 410
Hydrocortisone, *320*, 321
  adrenocortical effects of, 54t
  before amphotericin B administration, 226
  constant IV infusion rate for, 769t
  dosage for, 317t, 626t, 747t
  for hypoadrenocorticism, 626t, 649
  parenteral solutions of, interactions with, 20t
  topical preparations of, 658t
Hydrogen ion pump, in gastric acid secretion, 489, *489*
Hydrogen ion pump inhibitors, for gastrointestinal ulceration, 491
    due to NSAIDs, 504, 505
Hydrogen peroxide, as germicide, 254
  dosage for, 484t, 747t
  for emesis induction, 485
  in tissue injury, 305, *305*
Hydrolysis, in drug metabolism, 10, *10*
Hydroxocobalamin, 108. See also *Vitamin* B_{12}.
  as lipotropic agent, 502
25-Hydroxycholecalciferol, *633*, 634
  for hypoparathyroidism, 634
Hydroxyethyl starch. See *Hetastarch (hydroxyethyl starch).*
Hydroxyurea, 343–344, 747t
Hydroxyzine, dosage for, 459t, 608t, 665t, 747t
  for behavioral modification, 468
  for respiratory disease, 608t
  for skin disease, 665t, 666
Hyoscine (scopolamine), 486–487, 762t
  transdermal administration of, 670
Hyperactivity, 468, 471
Hyperadrenocorticism, 644–648
  complications of, 648
  diabetes mellitus with, 641, 647
Hyperadrenocorticism *(Continued)*
  diagnosis of, 645–646
  insulin resistance in, 641
  pathophysiology of, 644–645
  treatment of, 646–648
Hyperalgesia, 406
Hyperbaric oxygen therapy, for osteomyelitis, 180
Hypercalcemia, due to calcitriol therapy in chronic renal failure, 540
  fluid therapy for, 94, 635
  furosemide for, 94, 521t, 524, 635
  in acute renal failure, 531
  in hyperparathyroidism, 635
  thiazides and, 523
Hypercalcemia of malignancy, 635
Hyperchloremia, 79, 86
Hyperchloremic metabolic acidosis, 81
Hypercoagulable state, in glomerular disease, 541
Hyperdynamic shock, 89–90, 588–589. See also *Septic shock.*
Hyperglycemia, adverse effects of, 637
  brain injury due to, 451
  insulin-induced, 640–641
  persistent, diabetes mellitus due to, 637
Hyperkalemia, 80, 80t
  due to potassium-sparing diuretics, 523
  due to spironolactone, 523
  electrocardiographic findings in, 531
  in acute renal failure, 530t, 531
  in hypoadrenocorticism, 80
    treatment of, 87, 626t, 649
  in urethral obstruction, 91
  treatment of, 87, 87t
Hypermagnesemia, 80–81
Hypernatremia, 78, 78t
  due to osmotic diuretics, 520
  treatment of, 86
Hyperosmolar nonketotic diabetes mellitus, 643
Hyperparathyroidism, primary, 635
  secondary, in chronic renal failure, 534t, 539–540, 635–636
Hyperphosphatemia, 80
Hyperphosphaturia, in hyperparathyroidism, 635
Hypersensitivity, 352–353
  contact dermatitis due to, 368
  hyposensitization therapy for, 669
  respiratory disease due to, 365
    in cats, 617–618
    in dogs, 618
  to antimicrobials, 144–145
  to asparaginase, 345
  to aspirin, leukotrienes and, 285
  to drugs, 43–44
    cutaneous, 52–53
  to fungal organisms, 222
  to β-lactam antibiotics, 157
  to tetracyclines, 169–170
  type I (immediate), 43–44, 352, *352*. See also *Anaphylaxis.*
    treatment of, 364–365
  type II (cytotoxic), 44, 352–353
    treatment of, 365–367
  type III (immune complex disease), 44, 353
    skin lesions in, 53
    treatment of, 367–368
  type IV (delayed), 44, 350, 353
    treatment of, 368
Hypertension, 585–586
  due to glucocorticoids, 327
  erythropoietin therapy and, 111
  furosemide for, 521t, 525
  hydrochlorothiazide for, 521t

Hypertension *(Continued)*
  in chronic renal failure, 534t, 538–539
  in glomerular disease, 541, 542
  in renal disease, 585
  intracranial, 451–453
    due to head injury, 451
    due to opioids, 411
    in hepatic encephalopathy, 509
  pulmonary, 620
    with mitral valve insufficiency, 581
Hyperthermia, 588
  brain injury due to, 450
  malignant, 588
    dantrolene for, 480
Hyperthyroidism, 629–632
  cardiomyopathy in, 585, 629–630
    treatment of, 631
  drug disposition changes in, 28–29
  hypertension in, 585
  pathophysiology of, 629–630
  treatment of, 630–632
Hypertrophic cardiomyopathy, 584–585
  negative chronotropes for, 579
Hyperventilation, for intracranial hypertension, 451
  respiratory alkalosis due to, 82
Hypervitaminosis D, 635
Hypervolemia, hyponatremia with, 79
Hypnosis, 407
Hypoadrenocorticism, 648–649
  acidemia due to, 81
  corrected hyperchloremia due to, 86
  glucocorticoids for, 326
  hyperkalemia due to, 80
    treatment of, 87, 649
Hypoalbuminemia, calculating deficit in, for plasma infusion, 104
  due to chronic diarrhea, 93
  in liver disease, 93
  in nephrotic syndrome, 91
Hypocalcemia, after surgery for hyperparathyroidism, 635
  due to excessive phosphorus administration, 87
  fluid therapy for, 93–94
  in acute pancreatitis, 511
  in acute renal failure, 531
  in hypoparathyroidism, 632–633
  parathyroid gland in response to, 632, *633*
Hypochloremia, 79, 86
Hypoglycemia, brain injury due to, 451
  fluid therapy for, 93
  in distributive shock, 90
  insulin-induced, in diabetes mellitus, 641, 643
Hypogonadism, 682t, 688
Hypokalemia, 80
  due to diarrhea, 93
  due to furosemide, 524
  due to thiazides, 522
    potassium citrate for prevention of, 526
  due to vomiting, 92
  in cardiac disease, 92
  in chronic renal failure, 536
  in diabetic ketoacidosis, 93, 642
  in liver disease, 93
  treatment of, 86–87, 87t
Hypomagnesemia, 80–81, 87
Hyponatremia, 78–79, 78t
  due to osmotic diuretics, 520
  furosemide for, 525
  in cardiac disease, 92
  treatment of, 86
Hypoparathyroidism, 632–635
Hypophosphatemia, 80
  in diabetic ketoacidosis, 93, 642

Hypophosphatemia *(Continued)*
  in hyperparathyroidism, 635
  treatment of, 87
Hyposensitization therapy, for allergy, 669
Hypotension, due to opioids, 411
  due to phenothiazines, 461
  with brain injury, 451
Hypothalamic hormones. See also specific hormones.
  reproductive, 677–678
Hypothalamic-pituitary-adrenal axis, *645*
  cytokine regulation of, 318
  drug reactions involving, 53–55, 54t
  in glucocorticoid regulation, 313–314, *314*
  suppression of, by glucocorticoid therapy, 55, 323, 327
Hypothermia, for head injury, 451–452
Hypothyroidism, 624–629
  drug disposition changes in, 28–29
  pathophysiology of, 624–625
  treatment of, 628–629
Hypoventilation, respiratory acidosis due to, 82
Hypovolemia, hyponatremia with, 79
Hypovolemic shock, 89, 588
  glucocorticoids for, 306, 325

I

Ibuprofen, 295
  dosage for, 284t, 747t
  gastrointestinal disease due to, 50, 287t, 295
  pharmacologic effects of, 287
Idarubicin, 340–341, 747t
Idoxuridine, *239*, 240, 748t
  for ocular herpetic infection, 247
Imidacloprid, 663
Imidazole derivatives, 223t, 227–229, 232t. See also specific drugs.
  for candidiasis, 233
  for dermatophytosis, 231
  structure-activity relationships of, *224*, 227
Imidocarb dipropionate, 748t
  for ehrlichiosis, 212
Imipenem, 152t, 156, 158
  bronchial penetration by, 182, 182t
  central nervous system toxicity of, 51, 51t
  dosage for, 177t
  efficacy of, pH and, 140
  for anaerobic infections, 216
  for chemotherapy-related infection, 335
  for peritonitis, 204
  for pyothorax, 184
  parenteral solutions of, interactions with, 20t
  pharmacokinetics of, 157
Imipenem-cilastatin, 155t, 748t
  minimum inhibitory concentrations for selected organisms for, 132t
  susceptibility test interpretation for, 135t
Imipramine, dosage for, 413t, 459t, 544t, 665t, 748t
  for hypercontractile bladder, 543t, 544
  for pain, 413t, 419
  for skin diseases, 665t, 668
  structure of, 462
Immobilization, for thoracolumbar disc extrusion, 453
Immune complex disease, 44, 353
  skin lesions in, 53
  treatment of, 367–368
Immune response, 349–353, 350t, *351*, *352*
  antigen presentation in, 350, *351*
  cellular, 350, *351*
  cellular components of, 350–351, *351*
  cutaneous, 192
  glucocorticoids' effects on, 318, *319*, 322t, 327

Immune response *(Continued)*
  humoral, 350–351, *351*
  intestinal, 201
  nonspecific components of, 349
  NSAIDs' effects on, 286
  soluble components of, 351–352
  viral effects on, 354
Immunodeficiency virus, feline, 238t, 248–249
Immunogenicity, of protein and peptide drugs, 391
Immunoglobulin(s), 351–352
  human, 362
    dosing regimen for, 354t, 748t, 749t
    for immune-mediated hemolytic anemia, 365
Immunomodulators. See *Biologic response modifiers;* specific agents.
Immunostimulants, 353, 360–364. See also *Biologic response modifiers;* specific drugs.
Immunosuppressants, 355–360. See also *Biologic response modifiers;* specific drugs.
  for glomerular disease, 541
  indications for, 355
  principles of therapy with, 355
  with renal transplantation, 543
Incontinence, urinary, due to hypertonic bladder, 544t, 545
    due to hypotonic urethra, 544t, 545–546
    hormonal therapy for, 682t, 687
Indandiones, as anticoagulants, 121
  as rodenticides, 117, 121
Indomethacin, 295
Infections. See also *Antimicrobial therapy;* specific infections.
  bacterial, 175–219. See also *Bacterial infections;* specific infections.
  cancer chemotherapy and, 334–335
  colonization vs., 129, 130
    in external ear, 196
    in skin, 191
  fungal, 222–234. See also *Fungal infections;* specific infections.
  glucocorticoid therapy and, 327–328
  helminth, 267–277. See also *Heartworm disease; Helminth infections.*
  nosocomial, 130
  organisms causing, by site, 127t–128t
    identification of, 126–139
  polymicrobial, combination antimicrobial therapy for, 147–148, *147*
  protozoal, 258–265, 258t, 507. See also specific infections.
  rickettsial, 211–213, 506
  viral, 237–249. See also *Viral infections;* specific infections.
Infectious tracheobronchitis, 183, 238t, 246, 616–617
Infective endocarditis, 127t, 202–203
Infertility, due to anticancer drugs, 336
  idiopathic, inappropriate hormonal therapy for, 688–689, 688t
Inflammation, at infection site, 139, *140*
  glucocorticoids' effects on, 316, 317t, 318, *318*, 322t
  heparin's influence on, 119
  in osteoarthritis, 296
  in pyoderma development, 192
  β-lactam antibiotic penetration and, 157
  mediators of, in respiratory disease, *604*, 605–606, 605t
  pathophysiology of, 281–282, *282*, 283t
Inflammatory bowel disease, 368, 508–509
  cyclosporine for, 358
  glucocorticoids for, 324–325

Inflammatory bowel disease *(Continued)*
  sulfasalazine for, 498
Informed consent, 703–704
Inhibin, 678
Inhibitory quotient, 137–138, *138*
Initiation, in carcinogenesis, 43
Inosiplex, 243–244, 364
Inotropes. See also specific drugs.
  negative, 579
  positive, 573–579
    for shock, 590t, 591
"Ins and outs," fluid therapy using, in acute renal failure, 91
Insulin, adrenocortical effects of, 54t
  constant IV infusion rate for, 769t
  dosage for, 530t, 626t, 748t
  for diabetes mellitus, 626t, 637–640
    complications of, 640–643
  for diabetic ketoacidosis, 626t, 642–643
  for hyperkalemia, 87, 87t
    in acute renal failure, 530t, 531
    in hypoadrenocorticism, 626t, 649
  for propranolol toxicity, 571
  growth hormone's effects on, 649, 650
  hepatic effects of, 502–503
  in glucose regulation, 636
  in potassium regulation, 77
  parenteral solutions of, interactions with, 20t
  preparations of, 394, 626t, 637–638
  recombinant human, 392t, 394
  thiazide interaction with, 522
  thyroid effects of, 54t
Insulin resistance, 641–642
  due to growth hormone, 641, 649, 650
Integument. See *Skin* entries.
Interactions. See *Drug interactions.*
Interferon(s), 372–375. See also specific interferons.
  as antiviral agents, 244, 373
  natural, 373
Interferon α, 373
  as therapeutic agent in humans, 373
  for cancer, 375
  for feline infectious peritonitis, 247, 373–374
  for feline leukemia virus infection, 248, 374–375, 395–396
  for ocular herpetic infection, 247, 396
  in immune response, 350t
  recombinant feline, 373, 395
Interferon α2A, recombinant human, 392t, 395–396, 748t
Interferon β, 373
  as therapeutic agent in humans, 373
  for feline leukemia virus, 374
Interferon γ, 373
  as therapeutic agent in humans, 373
  for cancer, 375
  glucocorticoids' effects on, 306, 318, *319*
  in immune response, 350t
Interleukin(s), 375–376. See also specific interleukins.
  in immune response, 350t, 351, *351*
Interleukin-1, glucocorticoids' effects on, 306, 318, *319*
  in granulopoiesis, 113
  in immune response, 350, 350t, 351, *351*
  in septic shock pathogenesis, 304
  therapeutic use of, 375
Interleukin-1 receptor antagonist, 372
Interleukin-2, glucocorticoids' effects on, 306, 318, *319*
  in immune response, 350, 350t, *351*
  recombinant human, 392t, 396
  therapeutic use of, 375–376
Interleukin-3, in granulopoiesis, 113
Interleukin-3 *(Continued)*
  in immune response, 350t
Interleukin-6, 376
  in granulopoiesis, 113
  in immune response, 350t, 351, *351*
Interleukin-11, 350t, 376
International normalized ratio, for warfarin therapy, 122
Internet resources, 725t, 727t–728t
Interstitial cystitis, feline, 547–549
Intervertebral disc disease, muscle relaxants for, 480
Intervertebral disc extrusion, acute, 453–454
Intestines. See also *Gastrointestinal tract.*
  diseases of, 505–508
  factors facilitating infection in, 201–202
  motility and secretion in, 496, *497*
    drugs affecting, 496–501
  normal flora of, 127t, 201
  normal infection control mechanisms in, 201
  organisms causing infections of, 127t
Intoxications. See also specific toxic agents.
  resources on, 725t
  terminology of, 43
  treatment of, 717–725
    procedures for, 717t
Intracardiac injections, complications of, 592
Intracellular fluid, 75
  in geriatric animal, 30
  in pediatric animal, 32
Intracranial pressure, increased, 451–453
    due to head injury, 451
    due to opioids, 411
    in hepatic encephalopathy, 509
Intramedullary (intraosseous) administration, in cardiopulmonary resuscitation, 593
  of blood, 102
  of fluids, 85
Intramuscular administration, in pediatric animal, 31
Intraosseous administration, in cardiopulmonary resuscitation, 593
  of blood, 102
  of fluids, 85
Intraperitoneal administration, in pediatric animal, 31
  of blood, 102
  of fluids, 85
Intratracheal administration, in cardiopulmonary resuscitation, 592–593
Intravenous administration, drug interactions in, 18–19, 20t–21t
  of fluids, 84–85
  plasma concentration vs. time curve for, 4, *5*
  rates for, 775t–776t
Intravesicular agents, for lower urinary tract disease, 549–550
Introns, 386, *386*
Iodides, as antifungals, 231, 232t
  as expectorants, 613–614
  dosage for, 232t, 748t
  for hyperthyroidism, 631–632
  thyroid effects of, 54t, 55
Iodine, as germicide, 253–254
  dosage for, 626t, 748t
  for hyperthyroidism, 626t, 631–632
  for otitis externa, 197
  in thyroid hormone synthesis, 624, *627*
  radioactive, for hyperthyroidism, 631
    uptake of, in hyperthyroidism diagnosis, 630
Iodopate, for hyperthyroidism, 631
Iodophors, 253–254. See also *Povidone-iodine.*
  for surgical antisepsis, 256
  ototoxicity of, 52
Iohexol, 748t
Ionization, passive diffusion and, 5–6
Iontophoresis, 391
Iopamidol, 748t
Ipecac syrup, 485t, 748t
  for emesis induction, 485–486
Ipodate, 748t
Ipratropium bromide, 610
Ipronidazole, 507, 748t
Iron, 109–110, *109*, 716t
  in hemoglobin synthesis, 109
  in lipid peroxidation, 305
  intoxication with, 719t, 722t
  therapeutic use of, 110
    with erythropoietin, 111, 113
      for anemia of chronic renal failure, 540
Iron dextran, 110, 748t
  parenteral solutions of, interactions with, 20t
Irritable bowel syndrome, 507–508
Irritant(s), 661
Irritant receptors, in airway smooth muscle, 602–603
Ischemia, acute renal failure due to, 528
  cellular, sequelae of, 589
Isoerythrolysis, neonatal, 98
Isoetharine, 607, 608t
Isoflurane, 429–430, 748t
  in pediatric animal, 34
Isometheptene, 748t
Isoniazid, 155t, 748t
  for tuberculosis, 210
Isopropamide, 487, 488
  dosage for, 484t, 749t
Isopropanol, as germicide, 251
  intoxication with, 722t
Isoproterenol, antidiuretic hormone secretion and, 526
  as bronchodilator, *604*, 607, 608t
  as inotrope, 579
  constant IV infusion rate for, 769t
  dosage for, 562t, 608t, 749t
  in cardiopulmonary resuscitation, 592
Isoquinolones, 268t, 269t, 273–274. See also specific drugs.
Isosorbide, 520, 749t
Isospora infection, 258–261, 258t, *259*
Isotretinoin, *659*, 660, 661, 749t
Itraconazole, 227, 228
  cyclosporine interaction with, 356
  dosage for, 232t, 665t, 749t
  for aspergillosis, 234, 615
  for blastomycosis, 233
  for coccidioidomycosis, 234
  for cryptococcosis, 234
  for dermatophytosis, 231–232, 665t
  for histoplasmosis, 233, 507
  for *Malassezia* infection, 232–233
  spectrum of activity of, 223t, 227–228
  structure of, *224*
  therapeutic use of, 229
Ivermectin, 267–269, 268t, 269t
  central nervous system toxicity of, 50, 51t
  dosage for, 562t, 665t, 749t
  for demodectic mange, 674
  for heartworm disease, 562t, 597
    in cats, 598
  for heartworm disease prevention, 268–269, 562t, 597–598
    in cats, 598
  for *Otodectes*, 199
  for parasitic dermatoses, 665t, 668–669
  for parasitic lung disease, 619
  in combination anthelmintics, 276–277
  intoxication with, 722t
  topical, 663
  toxicity of, to collies, 50, 597, 598, 669

J

Jarisch-Herxheimer reaction, in Lyme borreliosis treatment, 209

Jenotone, 749t
Jugular vein, blood collection from, 100

K

Kanamycin, 155t, 160, 749t
  minimum inhibitory concentrations for selected organisms for, 132t
  parenteral solutions of, interactions with, 20t
  susceptibility test interpretation for, 135t
Kaolin, 505
Kaolin pectin, 484t, 499, 749t
Kennel cough, 183, 238t, 246, 616–617
Keratan sulfate, for septic arthritis, 181
Keratin, 655
Keratitis sicca, 357
Keratoconjunctivitis sicca, due to sulfonamides, 57, 168
Keratolytics, 657–659
Keratoplastics, 657–659
Ketamine, dosage for, 413t, 749t
  for anesthesia, 427–428
  for invasive procedures in critical illness, 420
  in pediatric animal, 34
  neuromuscular blockers' interactions with, 476t
  parenteral solutions of, interactions with, 20t
Ketoacidosis, diabetic, 82, 626t, 642–643
  fluid therapy in, 93, 642
Ketoconazole, 227, 228
  cyclosporine with, 356
    cost analysis of, 357–358
  dosage for, 232t, 626t, 749t
  drug interactions with, anticonvulsants, 434
    diazepam, 479
  for blastomycosis, 233
  for coccidioidomycosis, 234
  for cryptococcosis, 234
  for dermatophytosis, 231
  for histoplasmosis, 233, 507
  for hyperadrenocorticism, 626t, 648
  for *Malassezia* infection, 199, 232–233
  hormonal effects of, 55
  spectrum of activity of, 223t, 227
  structure of, *224*
  therapeutic use of, 229
Ketoprofen, 293–294
  adverse effects of, 287t, 294
  dosage for, 284t, 750t
  for endotoxic shock, 305
  for osteoarthritis, 297
  selectivity of, for cyclooxygenase isoforms, 284
Ketorolac, 284t, 294, 750t
Kidney. See *Renal* entries.
Kinins, in inflammatory response, *282*, 283t
Kirby-Bauer method, for culture and susceptibility testing, 130, *130*
Klebsiella pneumoniae, minimum inhibitory concentrations for selected antimicrobials for, 132t

L

Laboratories, for blood typing, 98
  for therapeutic drug monitoring, 71–72
Laboratory tests, drug interference in, 58
  heparin interference in, 120
Labyrinthitis, 178
β-Lactam antibiotics, 150–158, 151t. See also *Cephalosporins; Penicillin(s);* specific drugs.
  adverse effects of, 157–158
  central nervous system toxicity of, 51, 51t
  efficacy of, host factors affecting, 140
β-Lactam antibiotics *(Continued)*
  for anaerobic infections, 215–216
  in pediatric animal, 33
  mechanism of action of, 150–153, *153*
  parenteral solutions of, interactions with, 20t
  passive diffusion of, 5–6
  pharmacokinetics of, 157
  resistance to, 156–157
    in anaerobes, 215
  spectrum of activity of, 153–156
  structure of, *153*
  therapeutic use of, 158
Lactated Ringer's solution. See under *Ringer's solution.*
Lactation, drug disposition changes in, 35
Lactic acidosis, 81, 88
Lactitol, as cathartic, 500
  dosage for, 484t, 750t
  for hepatic encephalopathy, 509
Lactoferrin, 750t
Lactulose, as cathartic, 500
  dosage for, 484t, 750t
  for hepatic encephalopathy, 509
Large intestine. See also *Gastrointestinal tract; Intestines.*
  diseases of, 507–508
Laxatives, 499–500
Lazaroids, 306–307, *307*, 322
LD$_{50}$, defined, 43
Lead, intoxication with, 722t
Lecithin, 484t, 502
Leflunomide, 358–359
Lenperone, 750t
Leprosy, 196, 210
Leptospirosis, 208
Leucovorin (folinic acid), 109
  dosage for, 112t, 745t, 750t
  with methotrexate, 342
Leukemia, feline, 238t, 247–248
    interferon α for, 248, 374–375, 395–396
    zidovudine for, 243, 248
Leukocytes, antimicrobial concentration by, 140–141
  glucocorticoids' effects on, 316–318, 316t, *318*
  in immune response, 350–351, *351*
  in inflammatory response, 281–282, *282*
  lysis of, artifactual hyperkalemia due to, 80
  polymorphonuclear, in inflammatory response, 281, *282*
    NSAIDs' effects on, 285–286
Leukotrienes, drugs targeting, for respiratory disease, 610–611
  in inflammatory response, *282*, 283t, 284–285
  in respiratory tract inflammation, *604*, 605t, 606
  in septic shock pathogenesis, 304
Leuprolide, 681
Levallorphan, 750t
Levamisole, 268t, 271–272
  as immunostimulant, 363–364
  dosage for, 354t, 750t
  for eosinophilic granuloma, 367
  for heartworm disease, 597
  skin lesions due to, 53, 53t
Levarterenol, 750t
Levels of consciousness, in pain control, 407
Levo-amphetamine, 750t
Levodopa, 750t
Levothyroxine. See *Thyroxine.*
L-form bacterial infections, 207
Lick granuloma, 469, 673
Lidocaine, as antiarrhythmic, 563t, 570–571
  central nervous system toxicity of, 51t, 439, 570, 571
Lidocaine *(Continued)*
  cimetidine interaction with, 490
  constant IV infusion rate for, 769t
  dosage for, 413t, 563t, 750t
  for digitalis intoxication, 577
  for esophagitis, 503–504
  for gastric dilatation/volvulus, 505
  for head trauma, 453
  for pain, 413t, 419
  for shock, 590t
  for ventricular arrhythmia, 587
  for ventricular fibrillation, 593
  in critically ill patients, 420
  ototoxicity of, 52
  parenteral solutions of, interactions with, 20t
  structure of, *564*
  topical preparations of, 658t
Light, allergic drug reaction involving, 52
Lime sulfur, dosage for, 232t, 750t
  for dermatophytosis, 231, 674
  preparations of, 659t
  skin lesions due to, 53, 53t
Lime water, 750t
D-Limonene, 663
Lincomycin, 152t, 170
  dosage for, 155t, 750t
  neuromuscular blockers' interactions with, 476t
  susceptibility test interpretation for, 135t
Lincosamides, 151t, 170. See also specific drugs.
  in pediatric animal, 33
Linoleic acid, for canine seborrhea, 673
Linolenic acid, for pruritus, 672
γ-Linolenic acid (GLA), 666
  for pruritus, 672
  for skin disease, 667, 667t, 668
Linseed oil, 501
Liothyronine. See *Triiodothyronine.*
Lipid(s), dietary, in chronic renal failure, 535
  epidermal, 655
  hepatic accumulation of, drug-induced, 45
  metabolism of, glucocorticoids' effects on, 316
Lipid emulsion, amphotericin B preparation in, 227
Lipid mediators. See also *Leukotrienes; Prostaglandin(s).*
  drugs impairing, 305–307
  in septic shock pathogenesis, 304
Lipid peroxidation. See also *Oxygen radicals.*
  attenuation of, in neurologic injury, 306–307, *307*
  drugs blocking, 305–307
  in tissue injury, 304–305, *305*
Lipid-soluble drugs, absorption of, after topical administration, 22
  cross-species dose extrapolation for, 38
  in geriatric animal, 30, *30*
  in pediatric animal, 32
  metabolism of, 9–10, *10*
  volume of distribution of, 9
Lipocortin, 317, *317*
Lipopolysaccharide, external, in gram-negative organisms, 129, *129*
    antimicrobial penetration and, 143
    sepsis and, 205, *206*
Liposomal products, for biologic response modifier delivery, 378–380
  for protein and peptide drug delivery, 390
Lipotropic agents, for liver disease, 501–502
Lipoxygenase(s), in inflammatory response, *282*, 283t, 284–285
Lipoxygenase inhibitors, for respiratory disease, 610–611
Lisinopril, 565, 566

Lisinopril *(Continued)*
  dosage for, 534t, 563t, 750t
  for hypertension in chronic renal failure, 534t
Lithium, 750t
  adrenocortical effects of, 54t
  drug interactions with, furosemide, 524
    thiazides, 522
  thyroid effects of, 54t
Liver. See *Hepatic* entries.
Liver disease. See also specific diseases.
  bacterial, 127t, 510
  changes in drug disposition in, 26–27, 27t, *28*
  cholestatic, drug-induced, 45
    ursodeoxycholic acid for, 501
  drug-induced. See *Hepatotoxicity.*
  drugs for, 501–503
  due to heartworms, 594
  due to thiacetarsamide, 595
  fluid therapy for, 93
  glucocorticoids for, 325
  opioid pharmacokinetics in, 410
  treatment of, 509–511
  viral, 238t, 245–246
Loading dose, *14*, 15, 436
  calculation of, 64, *68*
  therapeutic drug monitoring and, 64–66, *65*
Lobaplatin, 750t
Lomustine (CCNU), 338, 750t
Loperamide, 416, 484t, 750t
  for diarrhea, 498
Loratadine, 611
Lorazepam, 445, 466
  dosage for, 459t
Lotions, 656
  for drug delivery, 658t
Lufenuron, 663, 750t
Lugol's solution, 253. See also *Iodine.*
  for hyperthyroidism, 631
Lung. See *Pulmonary* entries; *Respiratory system.*
Lupus erythematosus, 367
Luteal insufficiency, 682t, 685
Luteinizing hormone, 678–679, *678*
  commercial availability of, 681
  dosage for, 750t
  for estrus induction, 683
  measurement of, for timing hormone therapy, 684
Lyme borreliosis, 208–209
Lymphocytes, in immune response, 350–351, *351*
Lymphokine-activated killer cells, 375
Lymphoma, in feline leukemia virus infection, 248
  response of, to treatment, 332

M

MAC (minimum alveolar concentration), 429
Macrocyte formation, in vitamin B_{12} deficiency, 107
Macrolide antibiotics, 151t, 170. See also specific drugs.
  as anthelmintics, 267–270, 268t, 269t
  bronchial penetration by, 182
  for heartworm disease prevention, 597–598
  in pediatric animal, 33
  polyene, for fungal infections, 223–224
Macrophage(s), pulmonary intravascular, in respiratory defense, 604–605
Macrophage colony-stimulating factor, 394
Macrophage migration–inhibition factor, glucocorticoids' effects on, 317
Mafenide, 751t
Magnesium, disease-induced changes in, 80–81
  in commercial fluids, 85t
Magnesium chloride, for hypomagnesemia, 87
  for ventricular fibrillation, 593
Magnesium citrate, 500, 751t
Magnesium hydroxide, as antacid, 492
  as cathartic, 500
  dosage for, 484t, 751t
Magnesium oxide, 500, 751t
Magnesium sulfate, as astringent, 657
  as cathartic, 500
  constant IV infusion rate for, 769t
  dosage for, 484t, 751t
  for hypomagnesemia, 87
  for ventricular tachycardia, 593
  parenteral solutions of, interactions with, 20t
Maintenance dose, *14*, 15–16
Malassezia furfur, drug susceptibilities of, 223t
Malassezia pachydermatis, 232–233
  otitis externa due to, 199
Malathion, 663
Malignancy. See *Cancer; Neoplasia.*
Malignant hyperthermia, 588
  dantrolene for, 480
Mammary gland carcinoma, 682t, 687
Mandelic acid, for feline urologic syndrome, 547
Manganese, for osteoarthritis, 301
Mange, demodectic, generalized, 674
    ivermectin for, 665t
    milbemycin for, 665t, 669
Mannitol, 519t, 520
  adverse effects of, in thoracolumbar disc extrusion, 454
  as cathartic, 500
  constant IV infusion rate for, 769t
  dosage for, 521t, 530t, 751t
  for acute renal failure, 529–530, 530t
  for intracranial hypertension, 452
    in hepatic encephalopathy, 509
  for shock, 590t
  parenteral solutions of, interactions with, 20t
  structure of, *518*
  with amphotericin B, for toxicity reduction, 226
Marbofloxacin, 164, 165
  dosage for, 155t, 751t
  for bacterial pneumonia, 183
  for pyoderma, 194
  structure-activity relationship of, 162, *163*
Marijuana, intoxication with, 722t
Marking behavior, in cats, 471
  in dogs, 470
Mass exponent, for body surface area calculation, 16
Mast cell(s), airway, 605
Mast cell degranulation, immunoglobulin E in, 352
Mast cell growth factor. See *Stem cell factor.*
Mast cell stabilizers, for respiratory disease, 610
Mast cell tumors, glucocorticoids for, 326
MBC (minimum bactericidal concentration), 131, *131*
M-CSF (macrophage colony-stimulating factor), 394
Mean absorption time (MAT), 7
Mean arterial pressure, 586
Mean residence time (MRT), 13
Measurement, units of, conversions and equivalents for, 706–707
Mebendazole, 47, 269t, 751t
Mechanomyography, for evoked response measurement, in neuromuscular blockade monitoring, 478
Mechlorethamine, 751t
Meclizine, 484t, 486, *487*, 751t
Meclofenamic acid, 295
  adverse effects of, 287t
  dosage for, 284t, 751t
  selectivity of, for cyclooxygenase isoforms, 284
Medetomidine, 751t
  as preanesthetic medication, 427
  for emesis induction, 486
  for pain, 418–419
Medium-chain triglycerides, 751t
Medroxyprogesterone, 681
  dosage for, 459t, 751t
  for benign prostatic hyperplasia, 688
Megacolon, 508
Megaesophagus, 200, 503
Megaloblast formation, in vitamin B_{12} deficiency, 107
Megestrol acetate, 680, 681
  as appetite stimulant, 482
  as immunosuppressant, 354t, 359
  dosage for, 354t, 459t, 608t, 751t–752t
  for asthma, 618
  for benign prostatic hyperplasia, 688
  for estrus suppression, 685
Meglumine antimonate, 752t
Melarsomine, 268t, 275
  dosage for, 563t, 752t
  for heartworm disease, 595, 596–597
Melatonin, 752t
Melioidosis, 211
Meloxicam, 284t, 292, 752t
  selectivity of, for cyclooxygenase isoforms, 284
Melphalan, 337, 752t
  for feline infectious peritonitis, 247
Menadiol, 752t
Menadione (vitamin K_3), 117
  for rodenticide poisoning, 122
Menaquinone (vitamin K_2), 117
Meningitis, bacterial, 175–178, 177t
  steroid-responsive, 324
Menthol, 658t
Meperidine, 413t, 415–416, 752t
  in acute pancreatitis, 511
  monoamine oxidase inhibitor interaction with, 466
Mephenytoin, 450, 752t
Mepivacaine, 752t
Mercaptopropionyl glycine, 752t
Mercaptopurine, 752t
Mercury intoxication, 719t, 723t
Meropenem, 752t
Mesalamine (mesalazine), dosage for, 485t, 752t
  for diarrhea, 498–499
  for inflammatory bowel disease, 509
Mesna, 752t
Metabolic acidosis, 81–82, 81t
  due to carbonic anhydrase inhibitors, 521, 522
  in acute renal failure, 530t, 531
  in chronic renal failure, 534t, 536
  pathophysiology of, 77–78
  treatment of, 88
  with cardiac arrest, 592
Metabolic alkalosis, 81t, 82
  due to furosemide, 524
  pathophysiology of, 78
  treatment of, 88
Metabolism of drugs, 9–10, *10*. See also *Hepatic metabolism.*
  drug interactions involving, 23–24, 23t
  first-pass, bioavailability and, 6–7, *7*
      in liver disease, 27
    dosing regimen extrapolation and, 37

Metabolism of drugs *(Continued)*
  species and breed differences in, 35–36
Metabolites, measurement of, in therapeutic drug monitoring, 61
  pharmacologic activity of, 10
Metaldehyde, intoxication with, 722t
Metamucil, 752t
Metaproterenol, 607, 608t, 752t
Metaraminol, 752t
Metastasis, heparin's influence on, 119
Metergoline, 681
  for estrus induction, 679, 683–684
  for pregnancy termination, 687
Metformin, 644, 752t
Methanol, intoxication with, 722t
Methazolamide, 752t
Methemoglobinemia, 723t
  drug-induced, in cats, 36–37, 56, 56t
  due to urinary acidifiers, 526
Methenamine, 172
  dosage for, 155t, 752t
  for feline urologic syndrome, 548
  for urinary tract infection, 189
  thiazide interaction with, 522–523
Methicillin, 155–156, 752t
Methimazole, 626t, 752t
  for hyperthyroidism, 630–631
  hematologic disorders due to, 56, 56t
  thyroid effects of, 54t
Methionine, as lipotropic agent, 502
  dosage for, 485t, 521t, 752t
  for urine acidification in feline urologic syndrome, 547
  hematologic disorders due to, 56
Methocarbamol, 413t, 480, 753t
Methohexital, 427, 753t
  in pediatric animal, 34
Methoprene, 663
Methosulfone, for pruritus, 670
Methotrexate, 753t
  for cancer, 342
  for inflammatory bowel disease, 368
  for rheumatoid arthritis, 368
  for systemic lupus erythematosus, 367
Methoxamine, 753t
Methoxyflurane, 429, 753t
  hepatotoxicity of, 45
  nephrotoxicity of, 49, 429
Methscopolamine, 485t, 488, 753t
Methylbenzene. See *Toluene.*
Methylcellulose, 485t, 753t
Methylcobalamin, 108. See also *Vitamin* B_{12}.
Methylene blue, 753t
  hematologic disorders due to, 56, 56t
Methylphenidate, 459t, 468, 753t
Methylprednisolone, 321
  as antiemetic, 488
  constant IV infusion rate for, 769t
  dosage for, 317t, 354t, 665t, 753t
  for acute pancreatitis, 511
  for bacterial meningitis, 177
  for central nervous system trauma, 324
  for eosinophilic granuloma, 325, 367, 503
  for pruritus, 671
  for shock, 306, 325, 590t, 591
  for thoracolumbar disc extrusion, 454
  neuroprotective effects of, 306
  parenteral solutions of, interactions with, 21t
Methylprogesterone, for feline eosinophilic granuloma complex, 503
Methylpyrazole, 753t
Methylsulfonylmethane, 303
Methyltestosterone, *114*, 753t, 765t
Methylxanthines. See also specific drugs.
  as bronchodilators, 607–609, 608t
  for cardiac disease, 577
Metoclopramide, adrenocortical effects of, 54t
  as antiemetic, *487*, 488, 495
    in acute renal failure, 530t
    in chronic renal failure, 534t, 538
    in liver disease, 509
  as appetite stimulant, 482
  as prokinetic agent, 494–495, *494*, *495*
  central nervous system toxicity of, 51t, 495
  constant IV infusion rate for, 769t
  dosage for, 485t, 530t, 534t, 753t
  for acute gastritis, 504
  for gastroesophageal reflux, 504
  parenteral solutions of, interactions with, 21t
  seizures due to, 439
  structure of, *487*
Metoprolol, 563t, 572, 753t
  for mitral valve insufficiency, 581
Metritis. See also *Endometritis.*
  postpartum, 682t, 686
Metronidazole, 151t, 172
  bronchial penetration by, 182
  central nervous system toxicity of, 50, 51t
  dosage for, 155t, 485t, 754t
  fluorinated quinolones' synergism with, 200, 204
  for anaerobic infections, 216
  for antimicrobial prophylaxis in granulocytopenia, 218
  for bacterial overgrowth, 485t, 507
  for botulism, 217
  for cholangitis, 485t
  for giardiasis, 265, 485t, 507
  for *Helicobacter* infection, 505
  for hemobartonellosis, 213
  for hepatic encephalopathy, 509
  for inflammatory bowel disease, 508
  for oral cavity infections, 200
  for pentatrichomoniasis, 507
  for peritonitis, 204
  for stomatitis, 485t
  in pediatric animal, 33
  parenteral solutions of, interactions with, 21t
  spectrum of activity of, 152t, 172, 258t
  susceptibility test interpretation for, 135t
Metyrapone, 626t, 648
Mexiletine, 563t, 571, 754t
Mibefradil, 561
Mibolerone, 681, 754t
  for estrus suppression, 680, 685, 686
  for signs of pseudocyesis, 686
MIC. See *Minimum inhibitory concentration (MIC).*
Miconazole, 228, 232t, 754t
  topical, 659t, 662
Microbes, defined, 125
  immunostimulants derived from, 360–362
  resistance of, to germicides, 255
Microfilaremia, drug-induced anaphylaxis in, 43
Microminerals, 716t. See also specific minerals.
Microsporum species, drug susceptibilities of, 223t
Micturition, 542
  disorders of, 542–546, 543t
  inappropriate, in cats, 471
Midazolam, 413t, 426, 754t
  in pediatric animal, 34
Mifepristone, 680
Milbemycin, 268t, 269, 269t
  central nervous system toxicity of, 50, 51t
  dosage for, 563t, 665t, 754t
  for demodicosis, 663, 674
  for heartworm disease prevention, 269, 563t, 598
    in cats, 598
Milbemycin *(Continued)*
  for skin diseases, 665t, 669
  lufenuron with, 750t
Milk, drug diffusion into, 35
Milk of magnesia, 500
Milrinone, 563t, 577–578, 754t
  for dilated cardiomyopathy, 583
Mineral oil, 485t, 500, 754t
  topical preparations of, 658t
Mineralocorticoids, antidiuretic hormone secretion and, 526
  deficiency of, in hypoadrenocorticism, 648, 649
  physiologic effects of, 316, 318
  receptor for, 314–315
Minimum alveolar concentration (MAC), 429
Minimum bactericidal concentration (MBC), 131, *131*
Minimum inhibitory concentration (MIC), 131, *131*
  breakpoint, 131–136, *133*, 134t–135t
    dosage increase beyond, 135–136
  for antibacterial drugs, 132t
  for antifungal drugs, 223, 223t
  in relative efficacy evaluation, *133*, 136–137
  plasma drug concentration and, 137–139, *138*
Minimum lethal concentration, for antifungal drugs, 223
Minocycline, 169
  adverse effects of, 170
  bronchial penetration by, 182
  dosage for, 155t, 754t
  for ehrlichiosis, 212
  for Rocky Mountain spotted fever, 213
  susceptibility test interpretation for, 135t
Mismating. See *Pregnancy termination.*
Misoprostol, 681
  antihistamines with, for pruritus, 672
  dosage for, 485t, 530t, 534t, 754t
  for gastrointestinal ulceration, 491, 493
    due to NSAIDs, 288, 504
  for nausea and vomiting, in acute renal failure, 530t
    in chronic renal failure, 534t, 538
  protective effect of, for NSAID-induced renal damage, 48
    with piroxicam, 346
  with prostaglandin $F_{2\alpha}$, for pregnancy termination, 686
Mites, ear, 199, 665t
  ivermectin for, 665t, 669
Mithramycin (plicamycin), 635, 754t
Mitotane, 626t, 754t
  adrenocortical effects of, 54t
  for hyperadrenocorticism, 646–647
  thyroid effects of, 54t
Mitoxantrone, 341–342, 754t
Mitral valve insufficiency, 579–581
Mivacurium, 474t, 475
  recovery from blockade with, 478–479
Mixed bacterial vaccines, as immunostimulants, 361–362
Monensin, 754t
  for protozoal infections, 258t
  for toxoplasmosis, 263–264
Monitoring of drug levels. See *Therapeutic drug monitoring.*
Monoamine oxidase inhibitors, *458*, *460*, 465–466. See also specific drugs.
  tricyclic antidepressant interaction with, 464
Monobactam, *153*
Monoclonal antibodies, recombinant, 398
Monocytes, in inflammatory response, 282
Mononuclear phagocyte system, in respiratory defense, 604–605

Morphine, 412–414
  constant IV infusion rate for, 769t
  dosage for, 413t, 426t, 608t, 754t
  epidural administration of, 413t, 422
  for pulmonary edema, 581, 620
  for respiratory disease, 608t
  in critically ill patients, 420
  intoxication with, 723t
  parenteral solutions of, interactions with, 21t
  pharmacokinetics of, 410, 412–413
  receptor selectivity of, 409t
  structure of, *409*
Morphine mania, 410
Mothballs, intoxication with, 723t
Motion sickness, 483
  antiemetics for, 486–487, *487*
Moxalactam, 156
  for osteomyelitis, 181t
Moxidectin, 268t, 269–270
  dosage for, 563t, 755t
  for heartworm disease prevention, 269–270, 563t, 597, 598
  for skin diseases, 669
MRT (mean residence time), 13
Mucociliary apparatus, in respiratory defense, 603–604, *603*
Mucokinetic drugs, 613. See also *Acetylcysteine.*
Mucosal block phenomenon, in iron absorption regulation, *109*, 110
Mucous membranes, gold toxicity to, 360
  surgical preparation of, antiseptics for, 256
Multi-drug resistance, in inflammatory bowel disease, 508
  to cancer chemotherapy, 332
Multiple-animal households, behavioral problems in, 469
Mupirocin, 662
Muramyl dipeptide, 361
Muramyl tripeptide, 379
Muscarinic receptors, in airways, 609
  in gastrointestinal motility, 494, *494*, 496
Muscle, skeletal, glucocorticoids' effects on, 319, 326
  smooth, airway, control of tone of, 602–603, *603*
    heparin's effects on proliferation of, 119
    vascular, physiology of, 556–558, *557*, *558*
Muscle relaxants, 473–480. See also specific drugs and classes of drugs.
  centrally acting, 479–480
  for hypertonic urethra, 546
  monitoring with, 476–478, *477*, *478*
  peripherally acting, 480
Musculoskeletal system, bacterial infections of, 128t, 179–181
Mushrooms, intoxication with, 723t
Myasthenia gravis, 503
Mycobacterial cell wall extract, 755t
Mycobacterial infections, 196, 210–211, *211*
Mycophenolate mofetil, 358
  for myasthenia gravis, 503
Myelinolysis, due to aggressive correction of hyponatremia, 86
Myelosuppression. See also *Neutropenia.*
  due to cancer chemotherapy, 334–335
    body surface area and, 333–334
    granulocyte colony-stimulating factor for, 335, 377
  due to chloramphenicol, 170
  due to cisplatin, 344
  due to cyclophosphamide, 336–337
  due to felbamate, 449
  due to ganciclovir, 241–242
  due to phenobarbital, 441

Myelosuppression *(Continued)*
  due to sulfonamides, 168
Myocardial contractility, 553–555, *554*
  in heart failure, 559–560
Myocardial oxygen demand, determinants of, 556

N

Nadolol, 563t, 571, 755t
Nafcillin, 755t
  for osteomyelitis, 181t
Naftifine, 231
Nalbuphine, 417
  dosage for, 413t, 426t, 755t
  receptor selectivity of, 409t
Nalidixic acid, for urinary tract infections, 187t
Nalmefene, 459t, 755t
  for stereotypic behavior, 469
Nalorphine, 413t, 417, 755t
  receptor selectivity of, 409t
Naloxone, 417
  dosage for, 413t, 426t, 459t, 485t, 755t
  for behavioral modification, 468
  for psychogenic alopecia, 672
  receptor selectivity of, 409t
  septic shock and, 206
Naltrexone, 417, 665t, 755t
  for acral lick dermatitis, 673
  for behavioral modification, 468
  for skin diseases, 665t, 668
  for stereotypic behavior, 469
  pharmacokinetics of, 410
  receptor selectivity of, 409t
Nandrolone, dosage for, 112t, 534t, 755t
  for anemia, 115, 116
    in chronic renal failure, 534t, 541
  structure of, *114*
Naproxen, 284t, 294–295, 755t
Narcolepsy, 471
Narcotic. See also *Opioids;* specific drugs.
  defined, 408
Natamycin, 755t
Natriuretic, defined, 517
Nausea, drug-induced, 49–50
  in acute renal failure, 530t
Near drowning, 620–621
Nebulizer, drug delivery by, 613, 614–615, 615t
Necrosis, hepatic, drug-induced, 45
  skin, due to heparin, 120
  tissue, due to doxorubicin extravasation, 335, 340
Neo-Darbazine, 755t
Neomycin, dosage for, 155t, 755t
  for antimicrobial prophylaxis in granulocytopenia, 218
  for hepatic encephalopathy, 509
  for otitis externa, 197t, 199
  nephrotoxicity of, 160
  skin lesions due to, 53, 53t
  topical, 662
Neonatal colibacillosis, 202
Neonatal isoerythrolysis, 98
Neonates. See also *Pediatric animals.*
  blood-brain barrier permeability in, 32
  drug absorption in, 30, 31
  hepatic drug metabolism in, 32–33
  opioids' effects on, 412
Neoplasia. See also *Cancer.*
  feline viral. See *Feline leukemia virus infection.*
  gene therapy applications in, 398–399
  glucocorticoids for, 325–326
  immunomodulators in, 354
  interferons for, 375

Neoplasia *(Continued)*
  interleukin-2 for, 375–376
  liposomal muramyl tripeptide product for, 379
  piroxicam's effects on, 286, 294
Neostigmine, 479t, 755t
  for neuromuscular blockade reversal, 479
Nephrotic syndrome, 90
  diuretics for, 525
  fluid therapy for, 91
Nephrotoxicity, drug-induced, 47–49, 47t, 528–529
  in immune-mediated hemolytic anemia, 365
  mannitol for, 520
  of aminoglycosides, *42*, 48, 160–162, *161*
    furosemide and, 524, 529
  of amphotericin B, 49, 225–226, *225*
  of angiotensin-converting enzyme inhibitors, 48–49, 528, 566, *567*
  of cisplatin, 344
  of cyclosporine, 356
  of dimethylsulfoxide, 303
  of doxorubicin, 340
  of methoxyflurane, 49, 429
  of NSAIDs, 48, 288, 528
  of thiacetarsamide, 49, 595, 596
Nervous colitis, 507–508
Netilomicin, ototoxicity of, 52
Neuroleptics. See *Antipsychotic drugs;* specific drugs and classes of drugs.
Neurologic injury. See also *Central nervous system, trauma to.*
  due to vincristine, 339
Neuromuscular blocking agents, 473–479. See also specific drugs.
  depolarizing, 474–475
    mechanism of action of, 473–474, *474*
  dosage for, 474t
  drug interactions with, 476, 476t
  indications for, 474
  monitoring with, 476–478, *477*, *478*
  nondepolarizing, 475–476
    mechanism of action of, 473, *474*
  pharmacology of, 473–474, *474*
  reversal of, 478–479, 479t
Neuromuscular junction, anatomy and physiology of, 473, *474*
  monitoring of, during muscle relaxant use, 476–478, *477*, *478*
Neurons, resting membrane potential of, 431–432
Neurotoxicity, central. See *Central nervous system toxicity.*
  peripheral, of vincristine, 339
Neurotransmitters. See also specific neurotransmitters.
  in abnormal behavior, 457–458, *458*
  in appetite control, 482
  in vomiting reflex, 483, *486*
Neutropenia. See also *Myelosuppression.*
  antimicrobial prophylaxis in, 218, 334
  cyclic, granulocyte colony-stimulating factor for, 113
  immune-mediated, 366
Neutrophils, in inflammatory response, 281, *282*
  NSAIDs' effects on, 285–286
Niacin (nicotinamide), 714t
  dosage for, 354t, 755t
  for discoid lupus erythematosus, 367
Niclosamide, 755t
Nicotine, intoxication with, 723t
Nifedipine, 561, 564
Nifurtimox, 755t
Nikethamide, 755t
Nimesulide, 284

Nitrates. See also specific drugs.
  organic, as vasodilators, 566
Nitric oxide, in sepsis, 205
  in shock, 589
  in vascular smooth muscle contractility, 557–558, *558*
Nitric oxide synthetase, 557–558, *558*
  glucocorticoids' effects on, 317
Nitrofurans, 172. See also specific drugs.
Nitrofurantoin, 172
  dosage for, 155t, 755t
  for urinary tract infections, 187t
  parenteral solutions of, interactions with, 21t
Nitroglycerin, 566, 567
  dosage for, 563t, 755t
  for dilated cardiomyopathy, 584
  for pulmonary edema, 620
  transdermal administration of, 669, 670
Nitroprusside, 566
  constant IV infusion rate for, 769t
  dosage for, 563t, 755t
  for hypertension, 586
  structure of, *564*
Nitroscanate, 755t
Nitrosoureas, 338
Nitrous oxide, 429
Nizatidine, 485t, 505, 755t
  for gastroesophageal reflux, 504
  for gastrointestinal ulceration, *489*, 490
Nocardiosis, 209–210, 621
  factors interfering with antimicrobial action against, 139, *139*
Nociception, 405–406, *406*
Noise phobias, 470
Noncompliance, therapeutic drug monitoring in identification of, 61
Nonsteroidal anti-inflammatory drugs (NSAIDs), 283–295. See also specific drugs.
  adverse reactions to, 287–289, 287t, *288*, *289*
  central nervous system toxicity of, 51t
  chemistry of, 282
  dosage for, 284t
  drug interactions with, 287
    furosemide, 524–525
    methotrexate, 342
    potassium-sparing diuretics, 523
    thiazides, 522–523
  effects on articular cartilage, 286
  for diarrhea, 498–499
  for hyperthermia, 588
  for osteoarthritis, 297
  for postoperative pain, 420
  for pruritus, problems with, 673
  for respiratory disease, 611
  for sepsis syndrome, 207
  for shock, 90, 305, 590t, 591
  for thoracolumbar disc extrusion, 454
  gastrointestinal disease due to, 50, 287–288, *288*, *289*, 504–505
  hematologic disorders due to, 56, 56t, 288
  in critically ill patients, 421
  in geriatric animal, 29, 30
  intoxication with, 723t
  mechanism of action of, 282–286, *285*
  nephrotoxicity of, 48, 288, 528
  pharmacokinetics of, 286
  pharmacologic effects of, 286–287
  relative potency of, 287
  selectivity of, for cyclooxygenase isoforms, 284
Norepinephrine, 457, *458*, 755t
  constant IV infusion rate for, 770t
  in heart rate regulation, 567
  topical, for hemostasis, 116
Norfloxacin, 163, 165, 756t
Normal flora, 127t–128t
  anaerobes in, 213
  infection due to, 129–130
  of external ear, 196
  of gastrointestinal tract, 127t, 201
    prophylactic suppression of, 218
  of skin, in dogs, 191
Normosol, electrolyte composition of, 85t
Northern blotting, 387
Nortriptyline, 459t, 462, 756t
Noscapine, 612
Nose, fungal infections of, 615
Nosocomial infection, 130
Novobiocin, 155t, 171, 756t
Nucleic acid characterization, 387–388, *389*
Nutraceuticals, for osteoarthritis, 299–301
  regulation of, 299–300
Nutrition, 713t–716t
Nutritional support, in acute renal failure, 532
Nystatin, 662, 756t

O

Oatmeal, colloidal, 658t, 670
Obesity, insulin resistance due to, 641
  renal disease and, 535
Obsessive-compulsive disorders, 469
  acral lick dermatitis and, 469, 673
Obstructive shock, 89
Ocular disease, due to hypertension, 585–586
  glucocorticoids for, 326
  herpetic, 247, 396
  organisms causing, 128t
Ofloxacin, 155t, 756t
Oil, as ceruminolytic, 661
Ointments, 656, 657
Oliguria, defined, 90
  renal failure with, diuretics for, 529–531, 530t
    fluid therapy for, 90–91, 529
Olive oil, as cathartic, 501
Olsalazine, 485t, 756t
Omeprazole, 485t, 756t
  for gastrointestinal ulceration, 491
    due to NSAIDs, 288
  for ulcer prophylaxis with NSAID therapy, 505
  structure of, *487*
Oncogenes, 399
Ondansetron, *487*, 488
  dosage for, 485t, 756t
  with cancer chemotherapy, 335
o,p'-DDD. See *Mitotane*.
Ophthalmic disease, due to hypertension, 585–586
  glucocorticoids for, 326
  herpetic, 247, 396
  organisms causing, 128t
Opiates. See also *Opioids;* specific drugs.
  defined, 408
Opioids, 408–418. See also specific drugs.
  adrenocortical effects of, 54t
  adverse effects of, 410–412
  agonist, 412–416
    defined, 409
  antagonist, 417
    defined, 409
    for behavioral modification, 468
    for skin diseases, 668
    for stereotypic behavior, 469
  as analgesics, in acute pancreatitis, 511
  as antitussives, 611–612
  as preanesthetic medications, 426, 426t
  central nervous system toxicity of, 51t, 410–412
Opioids *(Continued)*
  defined, 408
  dosage for, 413t, 426t
  drug interactions with, 412
  endogenoes, 407, 408, *408*
    effects of, 410, 497–498
    in self-mutilation, 469, 673
  epidural administration of, 413t, 422
  fetal effects of, 410, 411
  for behavioral modification, 468
  for cranial trauma, 421–422
  for diarrhea, 498, 506
    in short bowel syndrome, 507
  for surgical pain, 420
  gastrointestinal effects of, 497–498
  immunomodulatory effects of, 353
  in critically ill patients, 420
  in geriatric animal, 29, 30, 410, 419
  in pediatric animal, 33–34
  indications for, 418
  intoxication with, 723t
  mechanism of action of, 408–410
  mixed agonist, 416–417
    defined, 409
    for behavioral modification, 468
  neonatal effects of, 412
  partial agonist, defined, 409
  pharmacokinetics of, 410
  physical dependence and tolerance with, 411-412
  receptors for, 408–409
    drug selectivity for, 409t
    in gastrointestinal tract, 497
  scheduling of, 411–412, 699, 699t
  structure of, *409*
  therapeutic use of, 417–418
Opiopeptins. See *Opioids, endogenous.*
Opium tincture, 756t
Oral administration, drug interactions in, 19–21, 22t
Oral cavity, disease of, 503
    bacterial, 200
    organisms causing, 127t
  normal flora of, 127t
Oral rehydration therapy, 202, 496
Orange Book, 699
Orbifloxacin, 155t, 165, 756t
  structure-activity relationship of, 162, *163*
Organophosphates, as anthelmintics, 268t, 269t, 273
  topical, as antiparasitics, 663
Orgotein (superoxide dismutase), 301–302
  dosage for, 284t, 756t
Ormetoprim, 260
  pharmacokinetics of, 168, 260
  resistance to, 167–168
  sulfonamides with. See *Sulfonamides, potentiated;* specific combinations.
Orphan drugs, 696
Osmolality, 75–76
  of commercial fluids, 85t
Osteoarthritis, 296–297
  disease-modifying agents for, 297–301, *301*, *302*
  glucocorticoids for, 324
Osteodystrophy, renal, 539
Osteomalacia, due to primidone, 442
Osteomyelitis, bacterial, 179–181, 181t
  organisms causing, 128t
Osteoporosis, due to glucocorticoids, 326
  due to heparin, 120
Osteosarcoma, response of, to treatment, 332
Otitis externa, 196–200, 197t, 198t
  acute, 198–199
  bacterial, 199
  ceruminous (seborrheic), 199–200

Otitis externa *(Continued)*
  chronic, 198
  glucocorticoids for, 323
  middle ear infection with, 178
  organisms causing, 128t
  pathophysiology of, 196
Otitis interna, 178
Otitis media, 178
Otodectes, 199
Ototoxicity, 51–52, 51t
  of aminoglycosides, 51–52, 162
  of furosemide, 52, 524
  otitis externa treatment and, 197
  otitis interna treatment and, 178
Ovarian cysts, follicular, 682t, 684–685
Over-the-counter drug, defined, 694
Ovulation, induction of, 682t, 684–685
Ovulation timing, 680
Owner noncompliance, therapeutic drug monitoring in identification of, 61
Oxacillin, 155–156
  dosage for, 155t, 756t
  for pyoderma, 194
  susceptibility test interpretation for, 135t
Oxazepam, as anxiolytic, 466
  as appetite stimulant, 482
  dosage for, 459t, 485t, 756t
  structure of, *434*
Oxfendazole, 756t
Oxibendazole, 268t, 271
  diethylcarbamazine with, 276
  hepatotoxicity of, 47
Oxidation, in drug metabolism, 10, *10*
Oxidized cellulose, as clotting matrix, 116, *116*
Oxybutynin, 544t, 756t
  for feline urologic syndrome, 548
  for hypercontractile bladder, 544
Oxycodone, 416
Oxygen demand, myocardial, determinants of, 556
Oxygen radicals. See also *Lipid peroxidation.*
  glucocorticoids as scavengers of, 306
  in inflammatory response, 283t
  in tissue injury, 304–305, *305*
  tissue damage due to, in shock, 589
Oxygen tension, tissue, antimicrobial efficacy and, 139t, 140
Oxygen therapy, for smoke inhalation, 621
  hyperbaric, for osteomyelitis, 180
Oxyglobin, 105
  in cardiopulmonary resuscitation, 590t
  interactions with, 21t
Oxymetholone, 112t, 756t
Oxymorphone, 410, 415
  dosage for, 413t, 426t, 756t
Oxytetracycline, 155t, 169, 756t
  parenteral solutions of, interactions with, 21t
Oxytocin, 678
  commercial availability of, 681
  constant IV infusion rate for, 770t
  dosage for, 756t
  for dystocia, 687
  parenteral solutions of, interactions with, 21t
Oxytriphylline, 607–609, 608t, 756t

P

Pacemaker tissues of heart, 556, *556*
Packed cell volume, blood dose calculated from, 102–104, 102t, *103*
Paclitaxel, 757t
Pain, acute, 405, 407
  chronic, 405, 407
  classification of, 405
  clinical recognition of, 407
  control of, 407–422. See also *Analgesia;* specific analgesic drugs and classes of drugs.
    dosages for, 413t
    endogenous, 407–408, *408*
    in cranial trauma, 421–422
    in critical illness, 420–421
    in geriatric animals, 419
    perioperative, 419–420
  mediators of, 406, *406*
  perception of, 406
  response to, 406–407
  surgical, 419–420
  transmission of, 405–406, *406*
Pamidronate, 635
Pancreas, disease of. See also specific diseases.
    fluid therapy for, 93
  in glucose metabolism, 636
Pancreatic enzymes, dosage for, 757t
  for exocrine pancreatic insufficiency, 511–512
  in short bowel syndrome management, 507
Pancreatic insufficiency, 511–512
  digestive enzymes for, 503
  histamine$_2$-receptor antagonists for, 491
Pancreatin, 485t, 503, 757t
Pancreatitis, acute, 511
    fluid therapy for, 93
  diabetes mellitus and, 639
  due to didanosine, 243
  glucocorticoid therapy and, 327, 328
Pancuronium bromide, 474t, 475, 757t
  constant IV infusion rate for, 770t
Panleukopenia, feline, 238t, 246
Pantothenic acid, 714t
Paradoxical acceleration, due to quinidine, 569
Paragonimus kellicotti infection, 619
Parainfluenza virus, canine tracheobronchitis due to, 238t, 246
Paralysis, pharmacologic, after head trauma, 453
Parasites. See also *Heartworm disease; Helminth infections;* specific drugs and classes of drugs.
  cutaneous, systemic drugs for, 665t, 668–669
    topical drugs for, 662–663
  pulmonary, 619
Parathyroid gland, diseases of, 632–636. See also specific diseases.
  in calcium homeostasis, 632, *633*
Paregoric, 757t
Parenteral administration. See also specific route.
  solutions for, drug interactions in, 18–19, 20t–21t
    pH of, drug disposition and, 19
Paromomycin, 757t
Paroxetine, 459t, 465, 757t
Partition coefficient, absorption of topical drugs and, 655
Partition ratio, for bronchial drug concentrations, 182
Parvaquone, 757t
Parvovirus enteritis, 238t, 244–245, 506
  fluid therapy in, 92, 245
Passive diffusion, drug movement by, 5–6
Peak plasma drug concentration, 67
  sample collection time for, *65*, 68, 70
Pediatric animals. See also *Neonates.*
  defined, 30
  drug disposition changes in, 30–33, 31t, *32*
  specific drug therapy for, 33–34
Pegaspargase, 345–346
Pemoline, 468
Pemphigoid, bullous, 366
Pemphigus, drug eruptions simulating, 53
  treatment of, 366–367
Penciclovir, 241
Penetration enhancers, for protein and peptide drugs, 390
D-Penicillamine, 757t
  for copper toxicity, 510
  for cystine urolithiasis, 521t
Penicillin(s), 153–156, 757t. See also β-*Lactam antibiotics;* specific drugs.
  aminoglycoside inactivation by, 19, 146
  bronchial penetration by, 182
  classification of, 151t, 153
  for actinomycosis and nocardiosis, 209
  for anaerobic infections, 215
  for botulism, 217
  for leptospirosis, 208
  for urinary tract infections, 187t
  international unit of, 155
  parenteral solutions of, interactions with, 20t
  pharmacokinetics of, 157
  structure of, *153*
  thyroid effects of, 54t
Penicillin G, 152t, 153–155
  dosage for, 155t, 177t, 757t
  for anaerobic infections, 215
  for urinary tract infections, 187t
  minimum inhibitory concentrations for selected organisms for, 132t
  parenteral solutions of, interactions with, 21t
  pharmacokinetics of, 157
  relative efficacy of, *133*
  susceptibility test interpretation for, 135t
Penicillin V, 155, 157
  dosage for, 155t, 757t
Penicillin-binding proteins, in bacterial cell wall, 150–153, *153*
Pennyroyal oil, 663
Pentamidine isethionate, 757t
Pentatrichomoniasis, 507
Pentazocine, 413t, 417, 757t
  for behavioral modification, 468
  receptor selectivity of, 409t
Pentobarbital, 757t
  constant IV infusion rate for, 770t
  for acute seizure management, 438, 450
  for head trauma, 452
  parenteral solutions of, interactions with, 21t
Pentosan polysulfate, 284t, 757t
  for osteoarthritis, 299
  for septic arthritis, 181
  for urinary tract infection, 189
Pentoxifylline, 303–304, 354t, 757t
  for dermatomyositis, 367
  for sepsis syndrome, 207
Peppermint-caraway oil, 504
Pepsin, 485t, 503
Peptide drug therapy, principles of, 390–391
Periactin, 485t
Perianal fistula, cyclosporine for, 354t, 357
Pericardial effusion, 587–588
Periodontal disease, 200
Peripheral nerve stimulation, for neuromuscular blockade monitoring, 476–478, *477*, *478*
Peripheral nervous system, in geriatric animal, 29
  injury to, due to vincristine, 339
Peristalsis, 493–494, *494*, 496. See also *Gastrointestinal tract, motility of.*
Peritoneal dialysis, 541, 542
  for peritonitis, 205
Peritonitis, 203–205
  feline infectious, 238t, 246–247
    interferon α for, 247, 373–374
    pericardial effusion in, 588
Permethrin, 658t
Perna mussel, 301

Pernicious anemia, 108
Peroxygen compounds, as germicides, 254
Perphenazine, 459t
Pertechnetate uptake test, in hyperthyroidism diagnosis, 630
Pethidine. See *Meperidine.*
Petrolatum, 757t
P-glycoprotein, in multiple-drug resistance, 332
pH, at site of infection, antimicrobial efficacy and, 139–140, 139t
  gastric, bacterial infection and, 201
    drug interactions involving, 22
  of parenteral solutions, drug disposition and, 19
  of urine. See also *Urine acidification; Urine alkalinization.*
    antimicrobial therapy for urinary tract infections and, 189
    drug interactions involving changes in, 24, 24t
    renal excretion rate and, 10, *11*
    therapeutic alteration of, 526–527
  passive diffusion and, 5–6
Pharmacokinetics, 3–13, *4–13.* See also *Disposition of drugs.*
  constructing profile of, from therapeutic drug monitoring data, *65, 68,* 70–71
    sample collection for, *65,* 68, 70
  drug interactions involving, 22–24, 22t–24t
  of maternal-fetal-placental unit, 34
  of protein and peptide drugs, 390
Phenamidine isethionate, 757t
Phenazopyridine, 189
Phenobarbital, 439–441, 757t
  acute toxicosis due to, 441
  adverse reactions to, *42,* 441
  central nervous system toxicity of, 51t
  dose modification with, 436–437, *437*
  drug interactions with, 434, 440–441
    carprofen, 291
    chloramphenicol, 64, 170, 434
    clorazepate, 434, 445, 446, 466
    cyclosporine, 356
    digoxin, 575
    felbamate, 449
    in therapeutic monitoring, 72t
    metronidazole, 265
    phenytoin, 434, 444
  for behavioral modification, 467
  for seizure management, acute, 437–438, 440, 446
    chronic, 439
  for tetanus, 217
  hematologic disorders due to, 56, 56t
  hepatotoxicity of, 45–46, *46,* 441
  parenteral solutions of, interactions with, 21t
  pharmacokinetics of, 433, 435, 435t, 440
  structure of, *433*
  therapeutic monitoring of, case studies of, 62, 64
    drug interactions in, 72t
    procedure for, 68
    reference data for, 63t
  thyroid effects of, 54t, 55, 441, 625, 629
Phenols, as germicides, *251,* 254
Phenothiazines. See also specific drugs.
  adverse effects of, 461
  as antiemetics, 487, *487*
    timing of administration of, 504, 505
  central nervous system toxicity of, 51t
  clinical indications for, 461–462
  drug interactions with, 461
    opioids, 412
    phenytoin, 444
  for pain, 418
Phenothiazines *(Continued)*
  for tetanus, 217
  pharmacologic effects of, 460–461
  seizures due to, 439, 461
  skin lesions due to, 53, 53t
  structure of, 460, *460*
Phenoxybenzamine, 544t, 757t–758t
  for feline urologic syndrome, 548
  for hypertonic urethra, 546
    with thoracolumbar disc extrusion, 454
Phentolamine, 758t
  constant IV infusion rate for, 770t
Phenylalanine mustard (melphalan), 337
  for feline infectious peritonitis, 247
Phenylbutazone, 292–293
  adverse effects of, 287t, 292, 293
  dosage for, 284t, 758t
  hematologic disorders due to, 56, 56t
  phenytoin interaction with, 444
  selectivity of, for cyclooxygenase isoforms, 284
  thyroid effects of, 54t
Phenylephrine, 758t
  as decongestant, 614
  constant IV infusion rate for, 770t
  for hypotonic urethra, 545
  parenteral solutions of, interactions with, 21t
Phenylpropanolamine, 543t, 758t
  adverse effects of, 545
  for hypotonic urethra, 545
  for urinary incontinence, 687
Phenytoin, 442–444
  as antiarrhythmic, 563t, 571
  dosage for, 563t, 758t
  drug interactions with, 434, 443–444
    cyclosporine, 356
    in therapeutic monitoring, 72t
    neuromuscular blockers, 476t
    phenobarbital, 434, 444
  for behavioral modification, 467
  for digitalis intoxication, 571, 577
  for tricyclic antidepressant poisoning, 464
  hepatotoxicity of, 45, 444
  parenteral solutions of, interactions with, 21t
  pharmacokinetics of, 433, 434, 443
  skin lesions due to, 53, 53t
  structure of, *433*
  thyroid effects of, 54t, 55
Phlebitis, due to anticancer drug extravasation, 335
Phosmet, 663
Phosphate. See also *Phosphorus.*
  dosage for, 626t, 758t
  for diabetic ketoacidosis, 642
  for hypercalcemia, 626t
  for hypophosphatemia, 87
  hyperparathyroidism in chronic renal failure and, 636
Phosphate enemas, 758t
  adverse effects of, 50–51, 501
Phosphodiesterase inhibitors, 577–578. See also specific drugs.
  as bronchodilators, 607
Phosphomethoxyethyl adenine, for feline immunodeficiency virus infection, 249
  for feline leukemia virus infection, 248
Phosphonoformic acid, 242, 746t
Phosphorus. See also *Phosphate.*
  dietary, in chronic renal failure, 535
  disease-induced changes in, 80
  hypocalcemia due to excessive administration of, 87
Phosphorus binders, for chronic renal failure, 534t, 535–536
Phthalysulfathiazole, 758t
Phycomycosis, 234, 507
Physical dependence, on opioids, 411–412
Physostigmine, 758t
  for ivermectin intoxication, 50, 268
Phytonadione (vitamin K_1), 117
  dosage for, 112t, 768t
  for rodenticide poisoning, 122
  parenteral solutions of, interactions with, 21t
Phytotoxins, 724t
Picrotoxin, 758t
  for drug-induced central nervous system toxicity, 50
Pilocarpine, 758t
Pimozide, 485t, 758t
Pindolol, dosage for, 459t
  for behavioral modification, 468
Pine oils, intoxication with, 724t
Pinocytosis, 6
Piperacillin, 156
  dosage for, 155t, 758t
  efficacy of, pH and, 140
  for anaerobic infections, 215, 216
  minimum inhibitory concentrations for selected organisms for, 132t
  susceptibility test interpretation for, 135t
Piperacillin-tazobactam, 762t
Piperazines, 268t, 269t, 272–273, 758t
Piroxicam, 284t, 294, 758t
  adverse effects of, 287t
  for cancer, 346, 549
Pituitary gland disorders, 649–651
  hypogonadism due to, 688
Pityrosporum (Malassezia) infection, 232–233
  otitis externa due to, 199
Placenta, drug movement across, 34–35, 190
Placental gonadotropins, 679
Plasma, for acute pancreatitis, 93, 511
  infusion of, 104
  platelet-rich, for immune-mediated thrombocytopenia, 366
  storage of, 101, *101,* 102t
Plasma clearance, 13, *13*
Plasma drug concentration, as stand-in for tissue concentration, 3
  determinants of, after fixed dose, 3–5, *4*
  fluctuation of, elimination half-life vs. dosing interval in, *14,* 15, *65*
  minimum inhibitory concentration and, 137–139, *138*
  peak, 67
    sample collection time for, *65,* 68, 70
  trough, 67
    sample collection time for, *65,* 68, 70
Plasma drug concentration vs. time curve, 3–5, *5*
  sample collection for determination of, 68
Plasma sterilization, 254
Plasmids, antimicrobial resistance mediated by, 143
  in recombinant technology, 387, *388*
Plastics, drug binding to, 19
Platelet(s), artifactual hyperkalemia due to lysis of, 80
  aspirin's effects on, 123
  heparin's effects on, 119
  interleukins' effects on, 376
  NSAIDs' effects on, 288
  storage of, 101, 102t
  vincristine-loaded, 101
Platelet-activating factor, glucocorticoids' effects on, 317
  in inflammatory response, *282,* 283t
  in respiratory tract inflammation, *604,* 606
Platelet-rich plasma, for immune-mediated thrombocytopenia, 366
Pleural disease, 621
Pleural lavage, for empyema, 621

Pleuritis, organisms causing, 127t
Pleurodesis, 621
Plicamycin (mithramycin), 635, 754t
Pneumonia, aspiration, 620
  bacterial, 183–184, 619
  mycotic, 619
Pneumonitis, allergic, 365
  in heartworm disease, 595
    in cats, 598
Poison. See also *Intoxications;* specific toxic agents.
  defined, 43
Polyarthritis, feline chronic progressive, 368
Polydipsia, due to glucocorticoids, 327
  primary (psychogenic), 79
Polyethylene glycols, 762t, 763t
  as vehicles for topical drugs, 657
Polyhydroxidine, for ear mites, 199
  for otitis externa, 197, 198t
Polymerase chain reaction, 387–388, *389*
Polymorphonuclear leukocytes, in inflammatory response, 281, *282*
  NSAIDs' effects on, 285–286
Polymyositis, 368
Polymyxin(s), 151t, 171–172, 763t
  for shock, 591
  neuromuscular blockers' interactions with, 476t
Polymyxin B, aerosol therapy with, 615t
  endotoxin binding by, 191
  for otitis externa, 197t
Polyphagia, due to glucocorticoids, 326
Polysulfated glycosaminoglycans, dosages for, 284t, 763t
  for osteoarthritis, 297–299
  for septic arthritis, 181
  for urinary tract infection, 189
Polyuria, defined, 90
  due to glucocorticoids, 327
  in healing phase of acute renal failure, 91
  renal failure with, fluid therapy for, 90
Porins, antimicrobial penetration into cells through, *129*, 143
Postantibiotic effect, 66, 137, *138*
Postpartum metritis, 682t, 686
Potassium, disease-induced changes in, 79–80, 80t
  for acute renal failure, 531
  for anorexia, 86
  for chronic renal failure, 536
  for diabetic ketoacidosis, 643
  for digitalis intoxication, 577
  for vomiting, 92
  in cardiac muscle action potential, 555, *556*
  in commercial fluids, 85t
  plasma concentrations of, reference range for, 79–80
  regulation of, 76–77
  renal transport of, 515–516, *516*, *517*
Potassium bromide, 446, 737t. See also *Bromides.*
Potassium chloride, 759t
  constant IV infusion rate for, 770t
  for chronic renal failure, 536
  oral, for hypokalemia, 86
  parenteral solutions of, interactions with, 21t
Potassium citrate, dosage for, 521t, 534t, 759t
  for calcium oxalate urolithiasis, 526
  for chronic renal failure, 534t, 536
  for urine alkalinization, 521t, 526
  with thiazide therapy, for hypokalemia prevention, 526
Potassium gluconate, 759t
  for chronic renal failure, 536
  for hypokalemia, 86
Potassium iodide, 759t
Potassium iodide *(Continued)*
  as expectorant, 613
  for hyperthyroidism, 631, 632
  supersaturated, for sporotrichosis, 234
  thyroid effects of, 54t
Potassium permanganate, 759t
Potassium phosphate, constant IV infusion rate for, 770t
  dosage for, 626t, 758t
  for diabetic ketoacidosis, 93, 626t, 642
  for hypophosphatemia, 87
Potassium sodium tartrate, as cathartic, 500
Potency, defined, 418
  of opioids, factors affecting, 418
Povidone-iodine, 253–254, 759t
  as antifungal, 231, 232t
  for hepatic encephalopathy, 509
  for nasal aspergillosis, 615
  for otitis externa, 197
  for peritonitis, 205
  for surgical antisepsis, 256
  for wound antisepsis, 256
Pralidoxime chloride, 763t
  parenteral solutions of, interactions with, 21t
Pramoxine, 658t
Praziquantel, 268t, 269t, 274, 759t
  for parasitic lung disease, 619
  in combination anthelmintics, 276
Prazosin, 566–567
  dosage for, 563t, 759t
  for feline urologic syndrome, 548
  for hypertension in chronic renal failure, 534t
  for hypertonic urethra, 543t, 546
Preanesthetic medications, 425–427
Prednisolone, 321
  cyclosporine with, after renal transplantation, 358
  dosage for, 317t, 354t, 563t, 608t, 626t, 665t, 759t–760t
  for allergic contact dermatitis, 368
  for asthma, 617
  for atopy, 323
  for central nervous system trauma, 324
  for chronic active hepatitis, 510
  for eosinophilic granuloma, 367
  for feline infectious peritonitis, 247
  for feline urologic syndrome, 548
  for hypercalcemia, 94
  for hypoadrenocorticism, 626t, 648, 649
  for immune-mediated hemolytic anemia, 365
  for inflammatory bowel disease, 324–325, 508
  for intraocular inflammation, 326
  for pemphigus, 366
  for pneumonitis, in heartworm disease, 598
  for pruritus, 671
  for septic shock, 306, 325
  for skin diseases, 665t
  for steroid-responsive meningitis, 324
  for thoracolumbar disc extrusion, 454
  trimeprazine with, 770t
  with mitotane therapy for hyperadrenocorticism, 647
Prednisone, *320*, 321
  dosage for, 317t, 354t, 759t–760t
  for asthma, 617
  for cancer, 346–347
  for feline eosinophilic granuloma complex, 503
  for feline urologic syndrome, 548
  for gingivitis and stomatitis, 325
  for hypoadrenocorticism, 649
  for immune-mediated hematopoietic disorders, 326
  for myasthenia gravis, 503
Prednisone *(Continued)*
  for osteoarthritis, 324
  for pruritus, 671
  for pulmonary granulomatosis, 620
  skin lesions due to, 53, 53t
Prefloxacin, 164
Pregnancy. See also *Fetus.*
  drug disposition changes in, 34–35
  endometritis treatment during, 190
  glucocorticoid therapy and, 328
Pregnancy termination, 682t, 686–687
  inappropriate hormonal therapy for, 688t, 689
Preload, effects of reduction of, 560
Prescription drugs, 701–702, 701t
  abbreviations used with, 709t
  defined, 694
Preservatives, in crystalloid solutions, adverse effects of, 84
Primaquine phosphate, 759t, 760t
Primidone, 441–442, 760t
  adverse reactions to, *42*, 442
  for behavioral modification, 467
  hepatotoxicity of, 45, 442
  pharmacokinetics of, 434, 435t
  structure of, *433*
  therapeutic monitoring of, data for, 63t
    drug interactions in, 72t
Probenecid, furosemide interactions with, 524–525
  thiazide interactions with, 322
Procainamide, 569–570
  constant IV infusion rate for, 770t
  dosage for, 563t, 760t
  for digitalis intoxication, 577
  for shock, 590t
  for ventricular arrhythmia, 587
  in gastric dilatation/volvulus management, 505
  metabolism of, 36
  parenteral solutions of, interactions with, 21t
  structure of, *564*
  therapeutic monitoring data for, 63t
Procaine, parenteral solutions of, interactions with, 21t
Procaine penicillin, 155t, 157, 757t
  for otitis externa, 197t
Prochlorperazine, 487
  dosage for, 485t, 760t
  for acute gastritis, 504
  isopropamide with, 751t
  parenteral solutions of, interactions with, 21t
Prodynorphin, *408*
Proenkephalin, *408*
Progestagens, synthetic, 680
Progesterone, 679–680
  acromegaly due to, 650
  commercial availability of, 681
  for luteal insufficiency, 685
  insulin resistance due to, 641
  serum concentration of, in ovulatory failure diagnosis, 684
Progestins, for behavioral modification, 467
Progression, in carcinogenesis, 43
Prokinetic agents, 494–496, *495*. See also specific drugs.
  as antiemetics, 488
  for megacolon, 508
Prolactin, 679
  neuroleptics' effects on, 461
  suppression of, for estrus induction, 683–684
Promazine, *487*, 760t
  parenteral solutions of, interactions with, 21t
Promethazine, 760t
  parenteral solutions of, interactions with, 21t

Promethazine *(Continued)*
  structure of, *487*
Promodulin, 354t, 364
Promotion, in carcinogenesis, 43
Proopiomelanocortin, 407, *408*
Propantheline, as antiarrhythmic, 573
  as antiemetic, *487*, 488
  dosage for, 485t, 543t, 760t
  for feline urologic syndrome, 548
  for hypercontractile bladder, 544t, 545
Propiomazine, 760t
Propionibacterium acnes, as immunostimulant, 361, 761t
    for pyoderma, 669
Propofol, 761t
  for acute seizure management, 438
  for anesthesia, 428
  for head trauma, 453
  neuromuscular blockers' interactions with, 476t
  parenteral solutions of, interactions with, 21t
Propoxyphene, 416
  phenytoin interaction with, 444
Propranolol, adverse effects of, *42*, 571
  as antiarrhythmic, 563t, 571
  dosage for, 459t, 534t, 563t, 761t
  drug interactions with, cimetidine, 490
    diazepam, 479
    furosemide, 524
  for behavioral modification, 468
  for hypertension in chronic renal failure, 534t, 539
  for hyperthyroid cardiomyopathy, 631
  for hypertrophic cardiomyopathy, 584, 585
  parenteral solutions of, interactions with, 21t
  thyroid effects of, 54t
Propylene glycol, as ceruminolytic, 661
  as vehicle for topical drugs, 657
Propylthiouracil, dosage for, 626t, 761t
  for hyperthyroidism, 626t, 630, 631
  hematologic disorders due to, 56, 56t
  thyroid effects of, 54t
Prostaglandin(s). See also specific prostaglandins.
  for immunomodulation, 363
  in inflammatory response, *282*, 283, 283t
  in respiratory tract inflammation, *604*, 605t, 606
  in septic shock pathogenesis, 304
  inhibition of synthesis of, in drug-induced nephrotoxicity, 48
    mechanisms of, 283–284, *285*
  thyroid effects of, 54t
Prostaglandin E, cytoprotective effects of, in gastrointestinal mucosa, 489, *489*, 491, *492*
  in gastric motility, 494
  in inflammatory response, 283
Prostaglandin F$_2$, adrenocortical effects of, 54t
  in respiratory tract inflammation, 605t
Prostaglandin F$_{2\alpha}$, commercial availability of, 681
  dosage for, 761t
  for estrus induction, 684
  for pregnancy termination, 680, 686
  for pyometra and postpartum metritis, 686
  in respiratory tract inflammation, 606
Prostatic carcinoma, 687
Prostatic hyperplasia, benign, 682t, 687–688
    inappropriate hormonal therapy for, 688t, 689
Prostatitis, bacterial, 190
Prosthetic devices, osteomyelitis and, 180–181
Protamine, 112t, 761t
  for heparin overdose, 117
Protectants, as vehicles for topical drugs, 657
Protein(s), as acid buffer, 77
  dietary, in acute renal failure, 532
    in chronic renal failure, 532–535
    in glomerular disease, 542
  metabolism of, glucocorticoids' effects on, 315–316
  plasma, in fluid deficit estimation, 83
Protein binding, antimicrobial therapy and, 143
  changes in, in liver disease, 27, 27t
    in renal disease, 25, 25t
  drug interactions involving, 22–23, 23t
  hepatic drug metabolism and, 10, 26
  hormonal drug effects involving, 55
  in geriatric animal, 30
  in pediatric animal, 32
  response to diuretics and, 518
  species and breed differences in, drug distribution differences and, 35
  volume of distribution and, 8–9, *9*
Protein drug therapy, principles of, 390–391
Protein hydrolysate, parenteral solutions of, interactions with, 21t
Protein-losing enteropathy, fluid therapy for, 93
Proteinuria, furosemide use in, 525
  limitations on diuretic response in, 518
Proteoglycans, in articular cartilage, 296
Proteus mirabilis, minimum inhibitory concentrations for selected antimicrobials for, 132t
Proton pump, in gastric acid secretion, 489, *489*
Proton pump inhibitors, for gastrointestinal ulceration, 491
    due to NSAIDs, 504, 505
Protooncogenes, 399
Protozoal infections, 258–265, 258t, 507. See also specific infections.
Protriptyline, 459t, 761t
  for narcolepsy, 471
Pruritus, chronic, 670–673
  drug-induced, 53
Pseudocyesis, 679, 680
  signs of, hormonal therapy for, 682t, 686
Pseudoephedrine, 608t, 614, 761t
Pseudomonas species, factors interfering with antimicrobial action against, 139
  minimum inhibitory concentrations for selected antimicrobials for, 132t
  otitis externa due to, 199
  relative efficacy of antibiotics for, *133*
Pseudopregnancy, 679, 680
  signs of, hormonal therapy for, 682t, 686
Psychogenic dermatoses, in cats, 472, 672
  in dogs, 470–471
Psychogenic polydipsia, 79
Psyllium, 485t, 761t
Pteroylglutamic acid. See *Folic acid.*
Ptyalism, due to anticholinergic agents, 544
Pulmonary arterial disease, in heartworm disease, 593–594
    treatment of, 594–595
Pulmonary disease, 618–621. See also *Respiratory system;* specific diseases.
  drug-induced, 56–57
  due to bleomycin, 341
Pulmonary edema, 620
  drug-induced, 56–57
  furosemide for, 524, 525
  in hypertrophic cardiomyopathy, 584
  with mitral valve insufficiency, 580–581
Pulmonary embolism, due to glucocorticoids, 327
  heparin for prevention of, 121
  in heartworm disease, 594
    in cats, 598
    pretreatment therapy for, 594–595
Pulmonary fibrosis, due to bleomycin, 341
Pulmonary hypertension, 620
  with mitral valve insufficiency, 581
Pulmonary infiltrates with eosinophils, 619–620
Pulmonary intravascular macrophages, in respiratory defense, 604–605
Pulsatile infusion device, for hormonal induction of estrus, 681, *683*
Pulse dosing, for pyoderma, antimicrobial resistance and, 195
Pure red cell aplasia, cyclosporine for, 358
Purgatives, 499–501
Purine nucleosides, as antiherpesvirus drugs, 240–242
Purpura, drug-induced, 53
Pus, 281
  antimicrobial efficacy and, 139, 139t
Pyelonephritis, 185. See also *Urinary tract infections.*
  bacterial, 189–190
Pyoderma, 191–196
  adjuvant therapy for, 195–196
  antimicrobial therapy for, 193–195, 664
    pulse dosing in, 195
    topical, 196
  immunomodulators for, 196, 669
  pathophysiology of, *191*, 192
  predisposing factors for, 191–192
Pyometra, 190–191, 682t, 686
Pyothorax, 184, 621
Pyrantel, 268t, 269t, 272, 761t
  in combination anthelmintics, 276–277
  levamisole interaction with, 272
Pyrethrins, 658t, 662, 663
  for ear mites, 199
  intoxication with, 724t
Pyrethroids, 662–663
Pyridostigmine, 479t, 762t
  for myasthenia gravis, 503
  for neuromuscular blockade reversal, 479, 479t
Pyridoxine (vitamin B$_6$), 714t
  phenytoin interaction with, 444
Pyrilamine maleate, 762t
Pyrimethamine, 762t
  sulfonamides with, for protozoal infections, 258t
    for toxoplasmosis, 263
Pyrimidine nucleosides, as antiherpesvirus drugs, 240
Pyriproxifen, 663
Pythiosis, 234, 507

Q

Quaternary ammonium compounds, *251*, 254, 255
  ototoxicity of, 52
Quinacrine, 485t, 762t
  for coccidioidomycosis, 507
  for coccidiosis, 261
  for giardiasis, 265, 507
Quinapril, 563t, 566
Quinidine, 569
  dosage for, 563t, 762t
  drug interactions with, digoxin, 569, 575
    thiazides, 523
  for atrial fibrillation, 587
  for ventricular arrhythmia, 587
  skin lesions due to, 53, 53t
  therapeutic monitoring data for, 63t
Quinolones. See also specific drugs.
  fluorinated, 151t, 162–166
    adverse reactions to, 166
    bronchial penetration by, 182

Quinolones *(Continued)*
  central nervous system toxicity of, 51, 51t
  drug interactions with, 166
  for antimicrobial prophylaxis in granulocytopenia, 218
  for brucellosis, 207
  for oral cavity infections, 200
  for peritonitis, 204
  for pyoderma, 194, 195
  for urinary tract infections, 187t, 188
  in pediatric animal, 33
  mechanism of action of, 163–164, *164*
  metronidazole synergism with, 200, 204
  pharmacokinetics of, 165–166, *166*
  resistance to, 165
  safety of, for developing fetus, 190
  seizures due to, 439
  spectrum of activity of, 152t, 164–165
  structure-activity relationship of, 162–163, *163*
  therapeutic use of, 166

R

Rabies vaccine, recombinant, 397
Radiation recall, with doxorubicin, 340
Radioactive iodine, for hyperthyroidism, 631
Radioactive iodine uptake test, in hyperthyroidism diagnosis, 630
Ranitidine, 505
  dosage for, 485t, 530t, 534t, 762t
  for gastrointestinal ulceration, *489*, 490, 491
    due to NSAIDs, 288
  for nausea and vomiting, in acute renal failure, 530t
    in chronic renal failure, 534t, 538
  hematologic disorders due to, 56t
  thyroid effects of, 54t
Reabsorption, from intestine, after bacterial degradation, 11, *12*
  from renal tubules, drug excretion and, 10, *11*
Reactive oxygen species. See *Lipid peroxidation; Oxygen radicals.*
Recombinant technology, 372, 383–399
  fundamentals of, 384–390, *386, 388, 389*
  future directions in, 398–399
  opposition to, 384
  procedures in, 387–390, *388, 389*
  products of, 372t, 390–398, 392t. See also specific products.
    principles of therapy with, 390–391
  safety in, 385
  tools of, 386–387
Rectal administration, in pediatric animal, 31, 33
  of fluid therapy, 33, 85
Red blood cell(s), changes in, during storage, 100
  formation of, 107–110, *108, 109*
  packed, storage of, 100–101, *101*, 102t
  parenteral solutions of, interactions with, 20t
Red blood cell count, glucocorticoids' effects on, 316
Red cell aplasia, cyclosporine for, 358
Red squill, intoxication with, 724t
Reduction, in drug metabolism, 10, *10*
Refractory period of cardiac muscle, 556
Refrigeration, parenteral solution shelf life and, 18–19
Regressin-V, 361
Regulation of drugs, 693–705. See also *Food and Drug Administration.*
  agencies involved in, 693, 693t, 694t
  laws and guidelines related to, 695t
    publication of, 693–694
Regulation of drugs *(Continued)*
  nutriceutical, 299–300
Rehydration, oral, 202, 496
Remission, 332–333
Renal amyloidosis, 541, 542
Renal blood flow, changes in, in cardiac disease, 28, 560
  diuretic therapy and, 518
  in pediatric animal, 32
  renal excretion rate and, 10, *11*
    in renal disease, 25
Renal disease. See also *Renal failure.*
  angiotensin-converting enzyme inhibitors for, 565–566
  changes in drug disposition in, 25–26, 25t
  chronic, anabolic steroids for anemia in, 115
    erythropoietin for anemia in, 111–112
  dialysis for, 542–543
  drug-induced. See *Nephrotoxicity.*
  furosemide use in, 525
  glomerular, 541–542
  hypertension in, 585, 586
  hypokalemia due to, 80
  obesity and, 535
  opioid pharmacokinetics in, 410
  transplantation for, 543
Renal excretion, in geriatric animal, 30
  in pediatric animal, 33
  of drugs, 10, *11*
    drug interactions involving, 24, 24t
    pathologic factors affecting, 25–26, 25t
    urinary tract infection therapy and, 187–188
  species and breed differences in, 36
Renal failure, acute, 528–532
    cellular protectants for, 532
    complications of, 532
    fluid therapy for, 90–91, 529, 531
    management of, 529–532, 530t
    mannitol for, 520, 529–530, 530t
    pathophysiology of, 528–529
  cardiac failure with, fluid therapy for, 92
  chronic, 532–541
    anemia in, 534t, 539–540
    anorexia and vomiting in, 534t, 538
    dietary strategies for, 532–536, 537t
    hyperparathyroidism in, 534t, 539–540, 635–636
    hypertension in, 534t, 538–539
    pathophysiology of, 532
    patient monitoring flowsheet for, *533*
  glucocorticoid therapy and, 328
  hyperkalemia due to, 80
  mannitol for, 520, 521t, 529–530, 530t
  metabolic acidosis in, 81
    in acute failure, 530t, 531
    in chronic failure, 534t, 536
Renal function. See also *Renal failure.*
  drugs affecting, 515–527
  fluid and electrolyte transport in, 515–516, *516, 517*
  glucocorticoids' effects on, 327
Renal osteodystrophy, 539
Renal transplantation, 543
  cyclosporine after, 358
Renal tubules, active drug transport in, 10, *11*
    in renal disease, 25–26
  passive reabsorption from, 10, *11*
Renin-angiotensin-aldosterone system, heparin's effects on, 120
  in heart failure, 559, *559*, 565
  in sodium regulation, 76
Reperfusion injury, 589
Replacement solutions, for fluid therapy, 84
Replication, 385, *386*
Reproduction, anticancer drugs' effects on, 336
Reproduction *(Continued)*
  glucocorticoids' effects on, 320
Reproductive hormones, 677–689. See also specific agents.
  commercial availability of, 681
  for hypotonic urethra, 545–546
  indications for rational use of, 681–688, 682t
  misuse of, 688–689, 688t
  physiologic principles of, 677–680
Reserpine, seizures due to, 439
Residence time, mean (MRT), 13
Resistance. See also specific drugs.
  in inflammatory bowel disease, 508
  to antifungal agents, 223
  to antimicrobials, 143–144
    pulse dosing and, 195
    topical therapy and, 145, 146
  to cancer chemotherapy, 332
  to fluorinated quinolones, 165
  to germicides, 255
  to glucocorticoids, 315
  to β-lactam antibiotics, 156–157
    in anaerobes, 215
  to sulfonamides, 167–168
Resorcinol, 659
Respiratory acidosis, 81t, 82
  pathophysiology of, 78
  treatment of, 88
Respiratory alkalosis, 81t, 82
  pathophysiology of, 78
  treatment of, 88
Respiratory depression, due to opioids, 410–411
Respiratory distress syndrome, acute, pulmonary edema in, 620
Respiratory system, 602–621
  defense mechanisms of, 603–605, *603*
  disease of, 615–621
    bacterial, 182–185, 182t, *183*, 616–617, 619
    feline viral, 238t, 247
    glucocorticoids for, 323–324, 608t
    organisms causing, 127t
  drug toxicity affecting, 56–57, 341
  drugs affecting, 606–615, 608t
  glucocorticoids' effects on, 319
  in geriatric animal, 29
  inflammation of, mediators of, *604*, 605–606, 605t
    pathogenesis of, 605
  normal flora of, 127t
  normal physiology of, 602–605, *603, 604*
Restriction endonucleases, 387
Restrictive cardiomyopathy, 585
Resuscitation, cardiopulmonary cerebrovascular, 591–593
Retinoids, 659–661, *659*
Retinol (vitamin A), 659, *659*, 714t
  canine distemper and, 245
  dosage for, 762t, 767t
Retroviruses, 238
  drugs active against, 242–243
Rheumatoid arthritis, 367–368
Rheumatoid factor, in infective endocarditis, 203
Rhinitis, allergic, 365
  organisms causing, 127t
Rhinitis medicamentosa, 614
Rhinosporidiosis, 234
Rhinovirus infection, in cats, 238t, 247
Ribavirin, 242, 762t
Riboflavin, 714t
  dosage for, 762t, 767t
Ribosomes, antimicrobials targeting, 141, *141, 152*

Rickettsial diseases, 211–213, 506
Rifampin, 151t, 171
  cyclosporine interaction with, 356
  dosage for, 155t, 177t, 762t
  for brucellosis, 207
  for tuberculosis, 210
  spectrum of activity of, 152t, 171
Rimantadine, 243
Ringer's solution, 762t
  electrolyte composition of, 85t
  lactated, 84, 752t
    electrolyte composition of, 85t
    for acidosis, 88
    interactions with, 21t
Rinses, antipruritic, 670
  for drug delivery, 656, 658t
RNA, 385–386, *386*
Rochelle's salt, 500
Rocky Mountain spotted fever, 212–213
Rocuronium bromide, 474t, 475
Rodenticide poisoning, hypercalcemia due to, 635
  vitamin K for, 117, 122
Roundworms, drugs for, in cats, 269t
    in dogs, 268t
Route of administration. See also specific routes.
  for antimicrobials, 142, 146
  for blood, 102
  for fluid therapy, 84–85
  for opioids, 410
  for protein and peptide drugs, 390–391
  in cardiopulmonary resuscitation, 592–593
Roxithromycin, 155t, 762t
"Rubber jaw," 539
Rubefacients, 661
Rutin, 762t

S

S-adenosylmethionine (SAMe), for liver disease, 502
  for osteoarthritis, 301
Safflower oil, for canine seborrhea, 673
Salicylates, 289–290. See also *Aspirin (acetylsalicylic acid).*
  intoxication by, acid-base disorder due to, 82
  spironolactone interaction with, 523
  thyroid effects of, 54t
Salicylic acid, topical, 658t, 659
Saline, for shock, 590t
  hypertonic, 84, 747t
    for hypovolemic shock, 89
  physiologic, electrolyte composition of, 85t
Saline diuresis, for hypercalcemia, 94
Salmon poisoning, 213, 506
Salmonella enteritis, antimicrobials for, 506
Salmonella typhimurium toxoid, for endotoxemia, 506
SAMe (S-adenosylmethionine), for liver disease, 502
  for osteoarthritis, 301
Scabies, ivermectin for, 665t, 669
Scalded skin lesion, drug-induced, 52
Schedule drugs, 411–412, 699, 699t
Scopolamine, 486–487, 762t
  transdermal administration of, 670
Scorpion sting, 724t
Seborrhea, canine, 673
Seborrheic otitis, 199–200
Sedation, after head trauma, 453
  defined, 407
  in pediatric animal, 33–34
Sedatives. See also specific drugs.
  for irritable bowel syndrome, 508
Sedatives *(Continued)*
  neuromuscular blockers' interactions with, 476t
Seizures, acute management of, 437–438
  brain injury due to, 450
  chronic control of, 438–439
  classification of, 432
  drugs capable of inducing, 50, 439
  drugs contraindicated for patients with, 439
  due to opioids, 411
  due to phenothiazines, 439, 460
  due to tricyclic antidepressants, 464
  glucocorticoid therapy and, 328, 439
  in bacterial meningitis, due to antimicrobial therapy, 178
  indications for treatment of, 431
  pathophysiology of, 431–433, *432*
Selamectin, 268t, 269t, 270, 762t
  for heartworm disease prevention, 270, 597, 598
Selective serotonin reuptake inhibitors, *458, 460,* 464–465. See also specific drugs.
Selegiline, 465–466, 762t
  for hyperadrenocorticism, 626t, 647, 648
  structure of, *460*
Selenious acid, 767t
Selenium, 716t
  as lipotropic agent, 502
  dosage for, 767t
  for acute pancreatitis, 511
  topical, 659t
    for canine seborrhea, 673
Selenium sulfide, 659, 659t
Self-mutilation, 469, 673
Senna, 762t
Separation anxiety, 470
Sepsis, 205–207, *206*
Sepsis syndrome, 205–207, *206*
  glucocorticoids for, 206–207, 325
Septic arthritis, 181
Septic shock, 89, 205–207, *206*
  dobutamine for, 206, 579
  glucocorticoids for, 306, 325
  in parvovirus enteritis, 506
  pathophysiology of, 304
Serotonin, 457, *458*
  in gastric motility, 494, *494*
  in inflammatory response, *282,* 283t
  in nausea and vomiting due to chemotherapy, 335
  in respiratory tract inflammation, *604,* 605t, 606
  in vomiting reflex, 483, *486*
Serotonin antagonists, as antiemetics, 488
    with cancer chemotherapy, 335
Serotonin reuptake inhibitors, selective, *458, 460,* 464–465. See also specific drugs.
Serotonin syndrome, 464
Serratia marcescens, in mixed bacterial vaccine, 361–362
  minimum inhibitory concentrations for selected antimicrobials for, 132t
  to induce myeloproliferation, 113
Sertraline, 465
  for acral lick dermatitis, 673
Serum separator tubes, drug binding to silicon gel in, 72
Serum sickness, 353
  drug-induced, 44
    skin lesions in, 53
Sesame oil, as carrier for antineoplastic agents, 345
Sevoflurane, 430
Sexual behavior, abnormal, in cats, 472
    in dogs, 470
Shampoos, antibacterial, for pyoderma, 670–671
Shampoos *(Continued)*
  antiparasitic, 662
  antipruritic, 658t, 670–671
  coal tar, 740t
    skin lesions due to, 53, 53t
  for canine seborrhea, 673
  for drug delivery, 656, 658t, 659t
  hypoallergenic, 658t
  with antimicrobial therapy for pyoderma, 196
Shape constants, for body surface area calculation, 16
Shark cartilage, 301
Shock, 588–593
  cardiogenic, 89, 588
  classification of, 588–589
  compensatory mechanisms in, 590
  distributive, 89, 588–589. See also *Septic shock.*
  fluid therapy for, 88–90, 590t, 591
  hemorrhagic, 89, 590t, 591
    glucocorticoids for, 306, 325
  hypovolemic, 89, 588
    glucocorticoids for, 306, 325
  in gastric dilatation/volvulus, 505
  inflammatory response modifiers for, 304
  obstructive, 89
  pathophysiology of, 589–590
  septic. See *Septic shock.*
  treatment of, 590–591, 590t
Shock organ, 43
Short bowel syndrome, 507
"Shotgun" preparations, for anemia, 110
SID (strong ion difference) system, 77
Sighthounds, drug disposition in, 37, *37*
Silicon gel, in serum separator tubes, drug binding to, 72
Silver nitrate, 762t
  intoxication with, 724t
  topical, for hemostasis, 116, *116*
Silver sulfadiazine, 762t
  for otitis externa, 197–198, 198t
Single twitch method, for neuromuscular blockade monitoring, 476, *478*
Sinoatrial node, action potential in, 556
Sinusitis, organisms causing, 127t
Skeletal muscle, glucocorticoids' effects on, 319, 326
Skin, drug absorption through, 655–656
    formulations for, 669–670
  drug-induced reactions in, 52–53, *52,* 53t
  immune response in, 192
  metabolic activity of, 654–655
  structure of, 654
  surgical preparation of, antiseptics for, 256
Skin diseases, 654–675. See also specific diseases.
  bacterial, 128t, 191–196
  glucocorticoids for, 323
  immune-mediated, 366–367
  systemic drugs for, 664–669, 665t
  topical drugs for, 657–663, 658t–659t
    vehicles for, 655–657
  treatment of, 670–675
Skin necrosis, due to heparin, 120
Skin So Soft, 762t
Slow-release preparations, species differences in absorption kinetics of, 35
  therapeutic concentrations with, 7, 15
Small intestine. See also *Gastrointestinal tract; Intestines.*
  diseases of, 505–507
Smoke inhalation, 621, 724t
Smooth muscle, airway, control of tone of, 602–603, *603*
  heparin's influence on proliferation of, 119

- Smooth muscle *(Continued)*
  - vascular, physiology of, 556–558, *557*, *558*
- Snake bite, 724t, 734t
- Socialization, stress and, 408
- Sodium, dietary, in chronic renal failure, 535, 538–539
    - in glomerular disease, 542
  - disease-induced changes in, 78–79, 78t
  - excessive administration of, in cardiac disease, adverse effects of, 91–92
  - in cardiac muscle action potential, 555, *556*
  - in commercial fluids, 85t
  - in extracellular fluid, osmolality and, 75, 76
    - renal regulation of, 515, 516
  - intestinal transport of, 496
  - regulation of, 76
  - renal transport of, 515–516, *516*, *517*
    - drugs interfering with, 523–524
- Sodium bicarbonate, constant IV infusion rate for, 770t
  - dosage for, 521t, 530t, 534t, 763t
  - for acidemia, 88
  - for ethylene glycol intoxication, 88
  - for hyperkalemia, 87, 87t
    - in acute renal failure, 530t, 531
  - for metabolic acidosis in chronic renal failure, 534t, 536
  - for shock, 590t
  - for tricyclic antidepressant poisoning, 464
  - for urine alkalinization, 521t, 526
  - in cardiopulmonary resuscitation, 592
  - parenteral solutions of, interactions with, 21t
  - with amphotericin B for toxicity reduction, 226
- Sodium bromide, 446, 737t. See also *Bromides.*
- Sodium carbonate, as antacid, 492
  - for emesis induction, 485
- Sodium chloride, as cathartic, 500
  - dosage for, 763t
  - for diabetic ketoacidosis, 642
  - for emesis induction, 485
- Sodium citrate, for collected blood, 100
- Sodium ethylenediamine tetra-acetic acid (EDTA), for hypercalcemia, 626t, 635
- Sodium hypochlorite (bleach), as antifungal, 231, 232t
  - as germicide, 253, 255
    - for dermatophytosis, 675
  - coronavirus susceptibility to, 247
  - for wound antisepsis, 257
  - ingestion of, 720t
  - parvovirus susceptibility to, 245
- Sodium iodide, 763t
  - for hyperthyroidism, 631
  - parenteral solutions of, interactions with, 21t
- Sodium nitroprusside. See *Nitroprusside.*
- Sodium phosphate, as cathartic, 500
  - dosage for, 758t, 763t
- Sodium polystyrene sulfonate, 763t
- Sodium stibogluconate, 763t
- Sodium sulfate, 500, 763t
- Sodium thiosulfate, 763t
- Solutions, calculations involving, 710–712
  - parenteral, drug interactions in, 18–19, 20t–21t
    - pH of, drug disposition and, 19
- Somatomedin C, growth hormone's effects on, 649
- Somatostatin, thyroid effects of, 54t
- Somatotropin. See *Growth hormone.*
- Somogyi overswing, 640–641
- Sorbitol, 763t
  - as cathartic, 500
- Sorivudine, 240
- Sotalol, 763t
- Southern blotting, 387, *389*
- Spasmolytics, 479–480, 496–497, *497*. See also specific drugs.
  - for feline urologic syndrome, 548–549
- Spastic colon, 507–508
- Spasticity, muscle relaxants for, 479–480
- Species differences, in drug disposition, 35–36
  - in target tissues, 36–37
  - therapeutic drug monitoring and, 71–72
- Spectinomycin, 763t
- Spider bite, 196, 724t
- Spinal cord. See *Central nervous system.*
- Spiramycin, 763t
- Spironolactone, 519t, 523–524
  - dosage for, 521t, 763t
  - for ascites, 511, 521t, 525
  - structure of, *518*
- Split estrus, 684
- Sporotrichosis, 223t, 234
- Spot-on products, for antiparasitic drug delivery, 662
- Sprays, antipruritic, 670
  - as vehicles for topical drugs, 656, 658t, 662
- Squalene, 661
- Stanozolol, dosage for, 112t, 534t, 763t
  - for anemia of chronic renal failure, 534t, 541
  - structure of, *114*
  - thyroid effects of, 54t
- Staphylococcal protein A, as immunostimulant, 361
- *Staphylococcus aureus*, minimum inhibitory concentrations for selected antimicrobials for, 132t
- *Staphylococcus aureus* phage lysate, 669, 763t
- *Staphylococcus intermedius*, pyoderma and, 191
- *Staphylococcus* species, defense mechanisms of, 192
  - factors interfering with antimicrobial action against, 139
  - relative efficacy of antibiotics for, *133*
- Status epilepticus, 432
  - management of, 437–438
    - diazepam for, 437, 445–446
    - pentobarbital for, 438, 450
- Stavudine, 243
- Steady state, therapeutic drug monitoring and, 62–67, *65*
  - time to, determinants of, *14*, 15
- Steam, for instrument disinfection, with infectious canine hepatitis, 246
- Stem cell factor, 113, 378
  - recombinant canine, 394
- Stereotypies, 469
- Sterilization, defined, 250
  - ethylene oxide, 253
  - plasma, 254
- Steroid(s). See also specific agents.
  - adrenal cortical. See *Glucocorticoid(s); Mineralocorticoids.*
  - anabolic, as hematinic drugs, 113–116
      - for anemia of chronic renal failure, 540
    - structure of, 113, *114*
    - thyroid effects of, 54t
  - for shock, 89–90
  - gonadal, 679–680
    - commercial availability of, 681
  - neuromuscular blockers' interactions with, 476t
- Steroid arthropathy, 324
- Steroid myopathy, 319, 326
- Stevens-Johnson syndrome, drug-induced, 52
- Stilbestrol, dosage for, 544t
  - for hypotonic urethra, 545–546
- Stimulants, for behavioral modification, 468
- Stomach. See also *Gastrointestinal tract.*
  - disease of, 504–505
- Stomatitis, 503
  - glucocorticoids for, 325
  - metronidazole for, 485t
- *Streptococcus pyogenes*, in mixed bacterial vaccine, 361–362
- Streptodornase, 122
- Streptokinase, 122
- Streptomycin, 155t, 764t
  - for brucellosis, 207
  - ototoxicity of, 52
- Stress, response to, 406–407
  - socialization and, 408
- "Stress leukogram," 316
- Strong ion difference (SID) system, 77
- Strontium poisoning, 725t
- Struvite urolithiasis, ammonium chloride for, 521t
- Strychnine poisoning, 480, 725t
- Styrid caricide, 764t
- Subcutaneous administration, in pediatric animal, 31
  - of fluid therapy, 85
- Succinylcholine, 474–475
  - dosage for, 474t, 764t
  - nondepolarizing neuromuscular blockers' interactions with, 476t
  - recovery from blockade with, 478–479
- Sucralfate, dosage for, 485t, 534t, 764t
  - for esophagitis, 503
  - for gastrointestinal effects of chronic renal failure, 534t, 538
  - for gastrointestinal ulceration, 493, *493*
    - due to NSAIDs, 288, 504
  - for ulcer prophylaxis, in absence of enteral nutrition, 504
  - structure of, *487*
- Sufentanil, 415, 764t
  - receptor selectivity of, 409t
- Sulbactam, β-lactam antibiotics combined with, 156, 157, 734t
- Sulfadiazine, 168, 764t
  - structure of, *167*
- Sulfadiazine-trimethoprim, dosage for, 155t, 764t, 766t
  - for coccidiosis, 261
  - for protozoal infections, 258t
  - for pyothorax, 184
  - for urinary tract infections, 187t
  - minimum inhibitory concentrations for selected organisms for, 132t
  - susceptibility test interpretation for, 135t
- Sulfadimethoxine, 260, 764t
  - amprolium with, 735t
  - for coccidioidomycosis, 507
  - for coccidiosis, 260
  - for protozoal infections, 258t
- Sulfadimethoxine-ormetoprim, dosage for, 155t, 764t
  - for coccidiosis, 260–261
  - for protozoal infections, 258t
  - for pyoderma, 194
- Sulfadoxine-pyrimethamine, for toxoplasmosis, 263
- Sulfaguanidine, 764t
- Sulfamerazine, 764t
- Sulfamethazine, 764t
  - susceptibility test interpretation for, 135t
- Sulfamethoxazole, 764t
  - adverse effects of, 168
  - bronchial penetration by, 182, 182t
  - pharmacokinetics of, 260
- Sulfamethoxazole-trimethoprim, cyclosporine interaction with, 356
  - dosage for, 177t, 764t

- Sulfamethoxazole-trimethoprim *(Continued)*
  - for coccidiosis, 261
  - for protozoal infections, 258t
  - minimum inhibitory concentrations for selected organisms for, 132t
  - relative efficacy of, *133*
  - thyroid effects of, 664
- Sulfanilamide, *167*
- Sulfaquinoxaline, 260
- Sulfasalazine, 168, 290
  - dosage for, 485t, 764t
  - for diarrhea, 498
  - for inflammatory bowel disease, 508–509
- Sulfhydryl groups, in feline hemoglobin, drug reactions and, 37
- Sulfisoxazole, 764t
  - for urinary tract infections, 187t
- Sulfobromophthalein sodium, 764t
- Sulfonamides, 151t, 167–169. See also specific drugs.
  - adverse effects of, 57, 168, 193, 260
  - central nervous system toxicity of, 51t
  - for anaerobic infections, 216
  - for coccidiosis, 258t, 259–261
  - for protozoal infections, 258t
  - hepatotoxicity of, 47
  - mechanism of action of, 167, *167*, 260
  - nephrotoxicity of, 49
  - parenteral solutions of, interactions with, 21t
  - pharmacokinetics of, 168
  - potentiated, 167–169
    - adverse effects of, 193
    - bronchial penetration by, 182
    - for actinomycosis and nocardiosis, 209, 210, 621
    - for antimicrobial prophylaxis in granulocytopenia, 218
    - for coccidioidomycosis, 507
    - for coccidiosis, 258t, 259–261
    - for empyema, 621
    - for pyoderma, 194
    - in pediatric animal, 33
    - mechanism of action of, 167, *167*, 260
    - pharmacokinetics of, 168
    - spectrum of activity of, 152t, 167, 258t
    - therapeutic use of, 168–169
  - pyrimethamine with, for protozoal infections, 258t
    - for toxoplasmosis, 263
  - resistance to, 167–168
  - skin lesions due to, 53, 53t
  - spectrum of activity of, 152t, 167, 258t
  - therapeutic use of, 168–169
  - thyroid effects of, 54t, 55, 168, 193, 629, 664
- Sulfonation, in drug metabolism, 10, *10*
  - species differences in, 36
- Sulfonylureas. See also specific drugs.
  - for diabetes mellitus, 643–644
- Sulfur, topical, as antifungal, 659t, 662
  - as antiseborrheic, 657–659, 658t
- Sulfur granules, in actinomycosis, 209
- Sunflower oil, for canine seborrhea, 673
- Sunlight, allergic drug reaction involving, 52
- Superoxide anion, in tissue injury, 304–305, *305*
- Superoxide dismutase (orgotein), 301–302
  - dosage for, 284t, 760t
- Supraventricular premature contractions, 586. See also *Arrhythmias.*
- Supraventricular tachycardias, 586–587. See also *Arrhythmias.*
- Suprofen, 764t
- Suramin, 243
- Surgery, antimicrobial prophylaxis for, 218–219
- Surgery *(Continued)*
  - antisepsis for, 255–256
  - fluid therapy before, 94
  - pain control with, 419–420
- Susceptibility testing. See *Culture and susceptibility testing.*
- Swimmer's ear, 200
- Switch process, with antidepressant therapy, 463
- Synergism, in antimicrobial therapy, 146–147, 147t
- Synovial fluid analysis, in arthritis diagnosis, 181
- Systemic inflammatory response syndrome, 89–90, 205. See also *Septic shock.*
- Systemic lupus erythematosus, 367

T

- T lymphocytes, in immune response, 350–351, *351*
- Tachycardias. See also *Arrhythmias.*
  - supraventricular, 586–587
  - ventricular, 587, 593
- Tacrolimus, 358
- Tamoxifen, 680, 764t
  - commercial availability of, 681
  - for mammary gland carcinoma, 687
  - thyroid effects of, 54t
- Tannic acid, topical, for hemostasis, 116
- Tapeworms, drugs for, in cats, 269t
  - in dogs, 268t
- Taurine, deficiency of, cardiomyopathy due to, in cats, 583
  - dosage for, 563t, 764t
  - for dilated cardiomyopathy in cats, 583, 584
- Tazobactam, piperacillin with, 758t
- Tea-tree oil, 663
- Teicoplanin, 155t, 764t
- Telazol (tiletamine-zolazepam), 764t
  - for anesthesia, 427, 428
- Telephone numbers, 727t–728t
  - for adverse drug reaction reporting, 699–701
  - for Center for Veterinary Medicine, 694t
  - for intoxication resources, 725t
  - of blood banking services, 99t
  - of blood typing laboratories, 98
  - of Professional Compounding Center of America, 698
- Temperature, environmental, subcutaneous drug absorption and, 31
- Teratogen, defined, 43
- Terbinafine, 231, 674–675
  - dosage for, 665t, 764t
- Terbutaline, as bronchodilator, *604*, *607*
  - dosage for, 608t, 764t
  - for bronchial disease, 617
  - thyroid effects of, 54t
  - with antimicrobial therapy for bacterial pneumonia, 184
- Terconazole, 229
- Terfenadine, 665t, 666, 764t
- Testosterone, 680
  - dosage for, 543t, 765t
  - for hypotonic urethra, 543t, 545
  - inappropriate use of, 688t, 689
  - structure of, *114*
- Testosterone cypionate, 543t, 765t
  - for hypotonic urethra, 545
  - for urinary incontinence, 687
- Testosterone enanthate, 112t, 765t
  - for hypotonic urethra, 545
- Testosterone propionate, 681
  - dosage for, 112t, 543t, 765t
  - for hypotonic urethra, 545
- Tetanic stimulation, for neuromuscular blockade monitoring, 477, *478*
- Tetanus, 216–217
  - muscle relaxants for, 480
- Tetanus toxoid, 765t
- Tetany, in hypoparathyroidism, 632–633
    - treatment of, 633–634
- Tetracaine, 419
- Tetracycline(s), 151t, 169–170. See also specific drugs.
  - adverse effects of, 169–170
  - antipruritic effect of, 671
  - dosage for, 155t, 354t, 765t
  - for discoid lupus erythematosus, 367
  - for ehrlichiosis prophylaxis, 212
  - for Rocky Mountain spotted fever, 213
  - for urinary tract infections, 187t
  - gastrointestinal disease due to, 50
  - iron interaction with, 110
  - nephrotoxicity of, 49
  - neuromuscular blockers' interactions with, 476t
  - parenteral solutions of, interactions with, 21t
  - skin lesions due to, 53, 53t
  - spectrum of activity of, 152t, 169
  - structure of, *159*
  - susceptibility test interpretation for, 135t
- Tetramine, 510, 765t
- Tetramisole, 765t
- Thallium, intoxication with, 725t
- Thenium closylate, 765t
- Theobromine, intoxication with, 720t
- Theophylline, *603*, *604*, 607–*609*
  - dosage for, 608t, 765t
  - drug interactions with, calcium channel blockers, 564
    - enrofloxacin, 69
    - fluorinated quinolones, 166
    - in therapeutic monitoring, 69, 72t
    - neuromuscular blockers, 476t
    - phenytoin, 444
  - for asthma in cats, 618
  - for bronchitis in dogs, 618
  - for cardiac disease, 577
  - for mitral valve insufficiency, 581
  - for pulmonary edema, 620
  - therapeutic monitoring of, 609
    - data for, 63t
    - drug interactions in, 69, 72t
  - with antimicrobial therapy for bacterial pneumonia, 184
- Therapeutic drug monitoring, 60–72
  - artifacts in, 71–72, 72t
  - availability of, 71
  - case studies of, 62, 64, 66, 67, 69, 70
  - data for specific drugs, 63t
  - drug criteria for, 61
  - implementation of, 62–68
  - indications for, 61
  - interpretation of data from, 68–71
  - rationale for, 60–61
  - sample collection for, artifacts due to, 72, 72t
    - for anticonvulsants, 435, 436
    - single-sample vs. two-sample, *65*, 67–68, 435
    - timing of, *65*, 68
  - with anticonvulsant therapy, 436–437, *437*, *438*
- Therapeutic factors, in antimicrobial dose calculation, 137–138, 145–146
- Therapeutic range, 3, *3*
  - individual variation in, 69–70, 71
  - therapeutic drug monitoring and, 61
- Thiabendazole, 228, 271, 765t
  - for ear mites, 199
  - for *Malassezia* otitis, 199
  - for otitis externa, 198